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BIOMARKERS AND ELECTROCONVULSIVE THERAPY IN LATE-LIFE DEPRESSION

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COLOFON
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BIOMARKERS AND ELECTROCONVULSIVE THERAPY IN LATE-LIFE DEPRESSION

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door

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Nieuws·gier·ig
bn, bw, (te)
verlangend te weten

- Van Dale

TABLE OF CONTENTS

Chapter 1: General introduction

Part I: Biomarkers and remission

Chapter 2: S100 calcium-binding protein B in older patients with depression treated with electroconvulsive therapy

Chapter 3: Inflammation and remission in older patients with depression treated with electroconvulsive therapy

Chapter 4: The pattern of inflammatory markers during electroconvulsive therapy in older depressed patients

Chapter 5: The course of apathy in late-life depression treated with electroconvulsive therapy

Part II: Biomarkers and cognition

Chapter 6: Inflammation and cognitive functioning in depressed older adults treated with electroconvulsive therapy

Chapter 7: Impact of inflammation on cognitive functioning after electroconvulsive therapy in older depressed patients with and without white matter hyperintensities

Chapter 8: Summary and general discussion

Chapter 9: Nederlandse samenvatting

List of publications
About the author
Dankwoord

CHAPTER 1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

"My psychiatrist advised that I start with ECT, well, I don't know, it probably won't work for me, and I am already quite forgetful"

Approximately 4.4% of the population worldwide is suffering from depression.[1] The symptoms of depression among which depressed mood, anhedonia, feelings of worthlessness, and suicidal ideation, are often recurrent and cause severe discomfort.[2] During the last decades, depression was ranked as one of the top leading causes of global disease burden.[3] In older age (55-74 years), the prevalence of depression tends to be higher 1 and older patients are more at risk of developing a chronic or recurrent depression than younger patients.[4–7] Late-life depression is associated with cognitive impairment, comorbid medical illness and increased risk of mortality.[8–10] Moreover, a study in the United States among older persons showed an increase of nearly 50% in healthcare costs for older persons with depression compared to older persons without depression.[11] Hence, the need for effective treatment is high, especially in older persons.

It is well known that a large number of patients does not respond to pharmacotherapy or psychotherapy.[12,13] Treatments using non-invasive brain stimulation such as electro-convulsive therapy (ECT) and transcranial magnetic stimulation (TMS) are therefore needed. Whereas studies on the efficacy of TMS for depression are growing, the effectiveness of ECT is already well established. It was demonstrated that ECT is more effective than other antidepressant treatments[14,15]: the overall remission rates of ECT range between 48 % and 66 %[16–18] for treatment resistant and non-treatment resistant depression, respectively. In comparison, the remission rate for antidepressant medication in older depressed patients lies around 37%.[13]

ECT uses an electrical current to induce an epileptic seizure of at least 20 seconds in duration (with a maximum of three minutes). During the procedure, patients receive an anaesthetic and muscle relaxant causing them to be asleep for five to ten minutes. ECT is applied twice or three times per week and a course of treatment takes an average of eight to 12 sessions.[19] In case of catatonia or suicidality, ECT can be administered daily, to induce a rapid response.[20] The picture below shows a typical ECT setup including a patient, ECT device, recording EEG and stimulating electrodes. The electrodes can be placed either right unilateral (RUL) or bilateral (BL) which means that one or two hemispheres of the brain are stimulated. Cognitive side-effects are lower in RUL, whereas the effectiveness may be higher in BL ECT.[14,16]

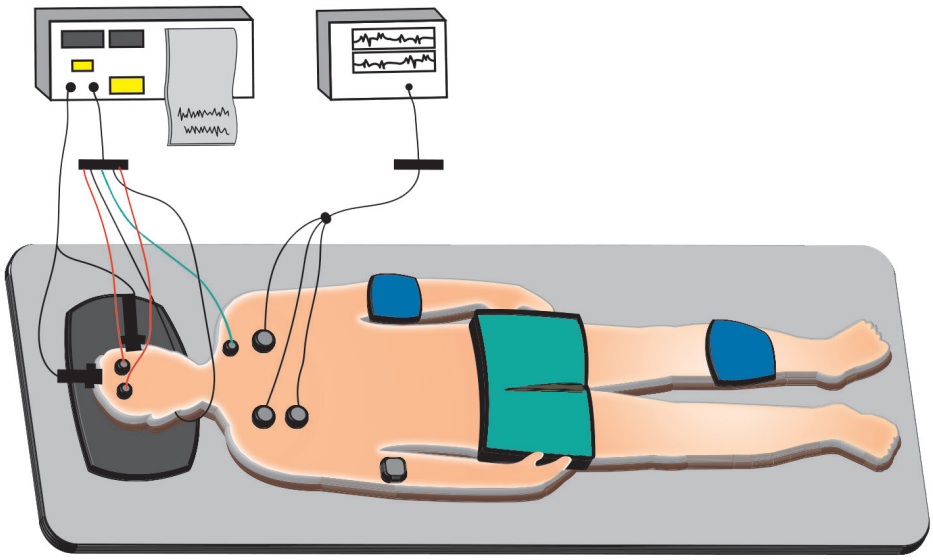

Figure 1: Graphical display of an electroconvulsive therapy setup

Despite its effectiveness, ECT is largely underused as a treatment for depression: merely 1.0% of all depressed patients receive ECT in the Netherlands.[21] The ECT administration rate, that is, the number of ECT administrations per 10.000 population per year, is used to compare ECT administration between countries. Compared to other countries the ECT administration rate in the Netherlands is low: 9.3 sessions per 10.000 inhabitants[22] compared to 11.2 sessions per 10.000 inhabitants worldwide.[23,24] Other European countries share these low ECT administration rates[25–28] and for example, in England, the use of ECT has declined over the past years.[29]

One contributing factor to these low numbers is that in many countries ECT is recommended in depressed persons only after two trials of antidepressants have failed[20] also defined as treatment resistant depression. Another factor is the remaining stigma around ECT[30] and the fear of side effects[31] not only in patients but also in practitioners. To improve the use of ECT and to get a more personalized depression treatment, further insight into which patients may benefit from ECT and which patients have the least risk of developing side effects is needed.

PART I:
Biomarkers and depression

Identification of markers associated with remission of depression could improve patient selection for ECT and improve remission rates. Years of ECT research have led to a set of clinical markers of patients most likely to respond to ECT, that is, older age, more severe depression, presence of psychotic features and less previous trials of pharmacotherapy failure[17,18,32,33]. As these markers have a low effect size, identifying additional (biological) markers is essential to further develop targeted treatment.[34] In this part of the thesis, we explore potential biomarkers of interest.

Immune response and neuroplasticity

First, ECT is thought to induce an initial immune activation followed by a downregulation (or normalization) of the immune system.[35] Depression itself is associated with elevated concentrations of inflammatory markers[36–40] and a decrease in inflammatory cytokine levels after treatment is associated with treatment response.[41,42] Therefore, in this thesis, inflammatory markers are further investigated for their potential function as markers of ECT outcome. Marker selection was based on their relevance in previous studies on inflammation and depression. C-reactive protein (CRP) is most widely used as a clinical marker for inflammation[43] and is often (in 30-50%) found elevated in depressed patients.[39] Both interleukin-6 (IL-6) and Tumour Necrosis Factor-alpha (TNF-α) are widely used in psychiatric research as potential biomarkers involved in depression.[44–46] Interleukin-10 (IL-10) is an anti-inflammatory cytokine[47] with strong deactivating properties of the inflammatory host response in case of excessive inflammation.[48] IL-10 is able to inhibit the production of proinflammatory cytokines such as IL-6 and TNF-α.[47]

Second, neurotrophic effects may play a part in ECTs working mechanism as volume increases in the anterior cingulate cortex have been observed after ECT.[49] In addition, it is thought that neuroplasticity is disrupted in depression.[50–52] S100 calcium-binding protein (S100B) is a protein that is expressed by astrocytes and oligodendrocytes. It has various functions in neuronal plasticity and apoptosis and can be used as a marker of neuroplasticity.[53] In this thesis, S100B is included as a potential biomarker of treatment outcome.

White matter hyperintensities

In addition, as previously described, older persons have a higher risk of developing chronic depression. It is known that apathetic symptoms can persist after depression

treatment[54] and that they can lead to a diminished quality of life.[55] Despite the difficulty of disentangling depressive symptoms like anhedonia from apathetic symptoms like a lack of motivation[56], apathy is thought to be an independent syndrome.[54,57] Small vessel disease - in brain imaging indicated by white matter hyperintensities - is increasingly suggested as a contributing factor to apathy[58–60] and is also more prevalent in late-life depression.[61] In this thesis, we examine depressive symptoms and apathy after a course of ECT. We explore whether patients with white matter hyperintensities are prone to developing persistent apathy and hence, a more unfavourable treatment course.

PART II
Biomarkers and cognition

As mentioned above, only a small number of depressed patients receive ECT. It is thought that the stigma surrounding ECT and the fear of side effects have contributed to the reluctance to ECT: ECT-related anxiety is found in 47% – 75% of patients eligible for ECT treatment.[31,62,63] Apart from the mild transient side effects such as nausea, headache and myalgia, (transient) cognitive side effects can occur after ECT.[64]

The cognitive side effects of ECT can be divided into three groups: postictal confusion, anterograde amnesia and retrograde amnesia. Postictal confusion frequently occurs after a single ECT session and it manifests as transient (minutes to hours) deficits in attention, memory and orientation.[64] Anterograde amnesia is the inability to create new memories. During a course of ECT patients often experience anterograde amnesia, for example, they will not remember some visits of doctors and family members. Retrograde amnesia means loss of memory of historical events. For example, some patients will, after a course of ECT, not be able to remember certain memories from the past: mostly from nonpersonal events and events that have occurred in the six months previous to ECT.[65] Retrograde amnesia is probably the most debilitating cognitive side effect of ECT.

Current known risk factors for lower cognitive functioning during and after ECT are poor baseline cognitive functioning and smaller hippocampal volume.[64,66,67] At present, it is impossible to identify which persons will experience cognitive side effects. Being able to recognize which patients are more prone to develop cognitive side effects is of clinical interest as it may lower fear for ECT and it may assist in developing strategies to minimize cognitive side effects. In this thesis, we examine cognitive functioning prior to,

during and after a course of ECT. We explore whether biological markers can assist in discovering which patients are more likely to experience cognitive side effects. At present, the mechanism behind cognitive impairment during ECT is unknown. Delirium is a syndrome characterized by a decline in cognitive functioning caused by an organic process. We have learned from delirium research that inflammation, endocrine abnormalities, and oxidative stress outside of the brain can lead to disturbances in cognitive functioning by interacting with degenerative changes inside of the brain.[68,69] In line with these findings, we hypothesize that patients with higher levels of peripheral inflammation experience lower cognitive functioning during and after ECT. In addition, the previously mentioned white matter hyperintensities – a degenerative change of the brain - are more common with advancing age.[70] Meta-analysis has found an association between white matter hyperintensities and progressive cognitive impairment.[71] Therefore, we want to look closer at white matter hyperintensities and their role in inflammation and cognition after ECT.

Aims and outline

This thesis aims to extent current knowledge on biomarkers in ECT-treatment in order to contribute to future personalized treatment of late-life depression. The first part aims to explore the pattern of biomarkers during a course of ECT and to explore the association between biological markers and treatment outcome. The second part aims to examine the association between inflammatory markers, cognitive functioning and white matter hyperintensities.

Chapter 2 examines the association between S100B and responsiveness to ECT. This chapter further concentrates on whether S100B reflects a state marker of depression. Chapter 3 examines the association between CRP, IL-6, IL-10, TNF-α and remission of depression. It further explores time to remission and speed of decline of depressive symptoms. In Chapter 4, the pattern of inflammatory markers throughout the course of ECT is examined. The pattern is compared between remitters, non-remitters, responders and non-responders. In Chapter 5 the persistence of apathy after ECT is examined in relation to white matter hyperintensities.

Chapter 6 explores whether baseline inflammatory biomarkers are associated with cognitive functioning prior to, during and after a course of ECT. Chapter 7 examines whether this association is different for patients with or without white matter hyperintensities. Finally, the clinical relevance of the findings, future implications and recommendations for future research are described in Chapter 8.

All chapters are based on data from the Mood Disorders in Elderly treated with Electroconvulsive Therapy (MODECT) naturalistic and longitudinal cohort study.[72] Between 2011 and 2013, 110 older patients (> 55 years) with a depressive disorder, all referred for ECT, were recruited in two tertiary psychiatric hospitals (GGZ inGeest, Amsterdam, the Netherlands and University psychiatric centre, KU Leuven, Belgium). Patients with a DSM-IV diagnosis other than a unipolar depressive disorder were excluded as well as patients with a history of a neurological illness including dementia, Parkinson's disease and stroke. The mean age of the sample was 73.0 ± 8.5 years and 66.4% were women. In 30.0% of patients, ECT was indicated because of life-threatening symptoms such as refusal of food and fluids or suicidality. More than half of the sample (58.2%) received ECT after previous pharmacotherapy resistance. Patients received ECT twice weekly according to Dutch guidelines.[20] ECT was continued until remission was reached (MADRS score < 10) or until no further improvement was seen for two consecutive weeks after a minimum of six unilateral and six bilateral ECT sessions. The response rate (50% improvement or more in MADRS score) was 78.2% and the remission rate was 66.4% after a mean number of 11.7 ± 5.4 ECT sessions. Before the start of ECT, baseline data were collected including demographics, physical comorbidities, medication use, depression severity, cognitive functioning, blood samples and magnetic resonance imaging (MRI). The mean depression severity was 33.6 ± 8.6 (severe depression) as measured with the Montgomery Åsberg Depression Rating Scale (MADRS). During ECT, information on depression severity, cognitive functioning and apathy was collected weekly. Blood samples were repeated after six ECT sessions and one week after finishing a course of ECT.

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Part I:
Biomarkers and remission

CHAPTER 2

S100 CALCIUM-BINDING PROTEIN B IN OLDER PATIENTS WITH DEPRESSION TREATED WITH ELECTROCONVULSIVE THERAPY

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Psychoneuroendocrinology, 2019

ABSTRACT

Background

Increasing evidence suggests that glial mediated disruption of neuroplasticity contributes to depression. S100 calcium-binding protein B (S100B) promotes neuronal protection in nanomolar concentrations. Studies on its possible role a a treatment outcome marker in affective disorders are limited. Recent evidence suggests a putative role for S100B as a state marker of illness activity as it is found elevated in episodes of major depression. The aim of this study was to investigate whether higher S100B is associated with favourable treatment outcome following electroconvulsive therapy (ECT) and to further explore whether S100B reflects a state marker of depression activity.

Methods

Serum S100B samples, at baseline and post-ECT and clinical assessments including Montgomery Åsberg Rating scales were collected in 91 older depressed patients (mean age: 73.0 years), referred for ECT. Change in pre- and post-ECT S100B was compared between remitters and nonremitters. Logistic and Cox regression analyses were used to determine whether S100B was associated with remission of depression.

Results

Patients with S100B levels in the intermediate tertile, that is, between 33 ng/L and 53 ng/L, had higher odds on remission, odds ratio: 5.5 (95%Confidence Interval (CI): 1.55-19.20, p = <0.01), and were more likely to remit from depression over time, hazard ratio: 1.96 (95%CI: 1.04-3.72, p = 0.04), compared with patients in the lowest tertile. There was no significant decrease in levels of S100B after ECT in both remitters and nonremitters.

Conclusion

Our findings demonstrate that patients with higher S100B levels at baseline were more likely to remit from depression suggesting an association between higher S100B and responsiveness to ECT. Next, S100B levels do not decrease after remission, suggesting S100B is not a state marker of depression. S100B is not capable of predicting treatment outcome by itself, further research may combine outcome markers.

INTRODUCTION

Unipolar depression is a severe mental illness with impact on cognitive and social functioning as well as quality of life.[1] Despite various treatment options available, a significant number of patients remain symptomatic. Hence, over the past years research has focused on finding putative predictors of treatment outcome. Possible markers including Brain Derived Neurotrophic Factor (BDNF), c-reactive protein (CRP), inflammatory cytokines and cortisol have been examined in previous studies, both in antidepressant treatment and electroconvulsive therapy (ECT).[2–5]

One protein of potential interest that seems to be involved in major depression is the S100 calcium-binding protein B (S100B).[6–8] This glial protein is located in the cytoplasm and nucleus of astrocytes and adipocytes exerting several intra- and extracellular functions. Intracellular, it has a regulatory role where it can stimulate cell proliferation and inhibit apoptosis and cell differentiation.[9] Extracellular effects of S100B are dose dependent. In the physiologic, nanomolar concentration range, S100B is thought to exert neurotrophic activity promoting neurite extension and protecting neuronal cells[10,11], whereas in micromolar concentrations (≥ 500 nM/L) S100B contributes to cell injury and increases neuroinflammation by activating microglia.[9,11] In addition, S100B is sometimes regarded as a marker for blood-brain barrier (BBB) permeability as it is found elevated in studies regarding BBB disruption.[12,13]

To date, the role of S100B in depression remains unclear. Previous studies examined S100B as a biomarker of treatment outcome. These studies suggest higher levels of serum S100B as a favourable feature in the course of disease. Higher baseline levels of S100B were associated with favourable ECT response in two studies[14,15] and in four other studies a better antidepressant treatment response in depressed patients with higher levels of S100B was reported.[16–19] In addition, a putative role for S100B as a state marker of illness activity has been suggested, based on elevated S100B levels that are consistently observed in major depression.[6,20] Notwithstanding the limited number of studies and small sample sizes, these results are promising and challenge us to further elucidate the association between S100B and depression.

Because of the high remission rates following ECT compared with antidepressant medication[21,22], we aim to investigate whether higher S100B is associated with remission of depression after treatment with ECT. Next, we aim to further explore whether S100B reflects a state marker of depression activity by monitoring levels pre-ECT compared with

post-ECT and investigating the association between S100B and severity of depression. Based on previous findings[14,15], we hypothesize that higher levels of S100B are associated with a favourable ECT outcome. Furthermore, if S100B is a state marker of depression, we expect a decline in S100B levels in remitted patients. The standardized procedures for the inclusion and treatment of patients in the Mood Disorders in Elderly treated with Electroconvulsive Therapy (MODECT) multicentre study, as well as for the collection and storage of serum samples, give us the unique opportunity to study S100B and treatment outcome in a relatively large sample of depressed patients treated with ECT.

METHODS

Subjects

The data for this study was derived from the multicentre study 'Mood Disorders in Elderly treated with Electroconvulsive Therapy' (MODECT) as described earlier.[23] MODECT included 110 patients, aged > 55 years, who fulfilled the DSM-IV criteria for major depression[24], as assessed by the Mini International Neuropsychiatric Interview (MINI)[25], and who were referred for ECT. All patients were recruited from an inpatient population at the department of Old Age Psychiatry of GGZ inGeest, Amsterdam, the Netherlands and the University Psychiatric Center KU Leuven, Belgium. Patients with a DSM-IV diagnosis of bipolar disorder or schizoaffective disorder were excluded from the study. Moreover, patients with established dementia or a major neurological illness were excluded. Written consent was obtained from all patients. The study protocol was approved by the ethical review board of the Amsterdam UMC and UPC Leuven and adhered the declaration of Helsinki.

S100B

Serum samples were collected between 07h30 and 09h30 and were stored at –85°C until assayed for S100B levels. Serum S100B values were determined using a chemiluminescence immunoassay (Elecsys ® S100) run on the Cobas 6000 analyser system (Roche Diagnostics), at the Endocrinology laboratory of the Department of Clinical Chemistry of the University Medical Center, VUmc, in Amsterdam, the Netherlands. Baseline and follow up samples of a patient were always assayed in 1 run. The S100B test had a measurement range from 0.005 µg/L to 39 µg/L. To facilitate interpretation, we present S100B in ng/L. In every run and after each system calibration, control samples of different concentrations were included, and results plotted in the QC system. Intra-assay variation (CV) was 1.3% and the inter-assay CV 4.6%. As the relation between levels of S100B and remission of depression was not linear,

serum S100B data was divided in categories. We additionally performed calculations to determine study size using Altman's nomogram.[26,27] We used an 80% probability of detecting differences in remission at a 5% significance level. The standardized difference was calculated using data from one earlier study investigating the relation between S100B and treatment outcome in depressed patients.[18] The calculations showed that it was sufficient to have 30 patients. We used tertiles (lowest tertile: ≤ 32 ng/L, intermediate tertile: 33 – 53 ng/L, highest tertile: ≥ 54 ng/L) in order to minimalize loss of information and to maintain sufficient group size (n ≈ 30). To evaluate the robustness of these findings, we repeated the analyses for dichotomized values of S100B, cut-off median value (low S100B: < 42 ng/L, high S100B: ≥ 42 ng/L).

Measures

Data were available at baseline (T0) and one week post-ECT (T1). Patients with missing values in depression severity at T0 and T1 and patients with missing S100B values on T0 were excluded from analyses (n = 16). Attrition was differential with respect to inclusion site, with a higher number of persons with missing serum samples in Amsterdam, The Netherlands. Attrition was not associated with age, sex, and depression severity. Depressive symptoms were assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS)[28], assessed prior to ECT, weekly during ECT and one week after ECT was ended (post-ECT). A semi-structured interview was performed to retrieve socio-demographics and clinical characteristics and included age, sex, body mass index (BMI), the use of antidepressant medication during ECT, and presence of cardiovascular diseases and malignant neoplasms. Several depression characteristics were examined, including depression severity (total MADRS score), treatment resistance, presence of psychotic symptoms, age of onset, duration of index episode of depression and recurrence of depression. Treatment resistance was defined as at least one trial with a score on the Antidepressant Treatment History Form (ATHF) of ≥ 3, representing adequate dose and duration of the trial.[29] Considering differences in definitions, an elaboration on the definition of medication resistance is available in the supplemental material. The presence of psychotic symptoms was assessed by a psychiatrist according to DSM-IV criteria[24], and confirmed by the MINI.[25] Early onset is defined as first episode before 55 years of age. Self-report was used for duration of index episode (in months) and recurrence of depression (at least one previous episode of depression).

ECT procedures

Patients were treated twice weekly with ECT, in accordance with Dutch Guidelines.[30] Seizures were induced by brief-pulse ECT (1.0 ms), administered by the Thymatron

System IV (Somatics, LLC, USA) with a maximum stimulus level of 1008 mC. Stimulus intensity was determined according to a dose titration protocol. A seizure of less than 20 seconds motor activity or less than 25 seconds EEG activity, was considered inadequate. Stimulation was changed to bilateral when clinical conditioned worsened or after six unilateral ECT sessions without improvement. Treatment was discontinued when patients reached remission, defined by a MADRS <10[28], or when no further improvement was achieved. After discontinuing ECT, the majority of patients received antidepressants (n=57/91) and add-on lithium (n=30/91). A small portion of patients received maintenance ECT (n=7).

Statistical analysis

All statistical analyses were performed using SPSS version 23. Group differences for continuous variables were analysed using independent samples t-tests (for normally distributed samples) and Mann-Whitney U tests (for nonnormally distributed values). For categorical variables, $\chi 2$ tests were used. Normality was examined using visual exploration of the data. Outliers (above 3x interquartile range) for S100B at baseline (n = 3) were excluded from analysis. Spearman's test for correlations was used to examine correlations between depression severity and S100B. Change scores (delta, Δ) of pre- and post-ECT S100B levels and MADRS scores were calculated by subtracting T0 from T1. Change scores were accordingly evaluated using Mann-Whitney U test. The association of S100B with remission of depression was examined using logistic regression analysis. Hazard ratio (HR) was examined using Cox regression analysis, with total number of received ECT sessions as time indication. The assumption of proportionality of hazard was checked. All analyses were adjusted for age. To develop an optimal covariate model from several variables a stepwise procedure was chosen for logistic regression. The covariates used for backwards regression analyses were depression severity, presence of cardiovascular disease, presence of malignant neoplasm, the use of antidepressant medication during ECT, duration of index episode, pharmacotherapy resistance, and presence of psychotic symptoms as these are suggested in current literature as putative confounders.[7,9,11,31,32] To check for multicollinearity the variation inflation factors (VIF) were calculated, where a VIF of ≥ 2 was considered as an indicator of multicollinearity.

Table 1. Sociodemographics, somatic morbidity and depression characteristics of the sample, across baseline S100B in older depressed patients treated with ECT.

	Total	**Lowest Tertile**	**Intermediate Tertile**	**Highest Tertile**	***p***
	n = 91	n = 30	n = 31	n = 30	
Sociodemographics					
Age, years, mean (SD)	73.0 (8.0)	71.8 (7.3)	73.8 (8.7)	73.3 (8.2)	0.6
Women, No. (%)	63 (69.2)	20 (66.7)	22 (71.0)	21 (70.0)	0.9
Baseline MADRS, mean (SD)	33.7 (9.1)	34.5 (9.0)	33.4 (7.1)	33.4 (11.0)	0.7
Decline in MADRS, median (IQR)	26.0 (16.0)	26.0 (24.0)	28.0 (10.0)	24.5 (18.5)	0.5
Antidepressant use during ECT, No. (%)	13 (14.3)	4 (13.3)	7 (22.6)	2 (6.7)	0.2
Inclusion site, Amsterdam, No.(%)	52 (57.1)	21 (70.0)	17 (54.8)	14 (46.7)	0.2
Number of ECT, mean (SD)	11.6 (5.0)	12.9 (6.2)	11.2 (4.7)	10.6 (3.7)	0.2
Somatic morbidity					
Cardiovascular disease, No. (%)	22 (24.7)	7 (24.1)	7 (23.3)	8 (26.7)	1
Malignant neoplasm, No. (%)	15 (16.9)	5 (17.2)	4 (13.3)	6 (20.0)	0.8
BMI, mean (SD), n = 61	23.4 (3.9)	21.8 (3.6)	23.6 (3.6)	24.6 (4.2)	0.1[1]

[1] p for trend = 0.01

SD = standard deviation, IQR = inter quartile range, No. = number, MADRS = Montgomery Åsberg Depression Rating Scale, BMI = body mass index

Table 1. Continuation

	Total	Lowest Tertile	Intermediate Tertile	Highest Tertile	*p*
	n = 91	n = 30	n = 31	n = 30	
Depression characteristic					
Psychotic, No. (%)	42 (46.2)	12 (40.0)	11 (35.5)	19 (63.3)	0.1
Medication resistant, No. (%),	56 (67.5)	14 (53.8)	21 (67.7)	21 (80.8)	0.1
Index episode, months, median (IQR),	6.0 (10.0)	6.0 (9.3)	6.0 (10.8)	6.0 (7.5)	0.9
Recurrence, No. (%)	70 (76.9)	23 (76.7)	25 (80.6)	22 (73.3)	0.8
Early onset, No. (%)	39 (42.9)	17 (56.7)	10 (32.3)	12 (40.0)	0.2
Serum S100B ng/L					
Pre-ECT, median (IQR)	42.0 (27.0)	25.0 (7.3)	42.0 (10.0)	70.5 (33.0)	<0.01
Post-ECT, median (IQR)	40.0 (30.0)	24.5 (14.3)	45.0 (14.5)	60.5 (35.3)	<0.01

SD = standard deviation, IQR = inter quartile range, No. = number

RESULTS

Subject characteristics

Baseline characteristics of the study population and the distribution across tertiles of S100B serum levels are shown in Table 1. The sample consisted of 91 older depressed persons, of which 69.2% patients were female, with a mean age of 73.0 years. Patients received between 4 and 29 ECT sessions (mean of 11.6 ± 5.0 (Standard Deviation)). The majority of patients received unilateral ECT (64.8%). Mean depression severity at baseline was 33.7 on the MADRS indicating severe depression. Median S100B at baseline was 42 ng/L. There were no significant differences between patients with different levels of S100B with respect to age, sex, depression severity or duration of treatment.

Table 2. Association between S100B (ng/L) and remission of depression in logistic regression analyses shown for tertiles in older depressed patients treated with ECT. Overall difference between tertiles p-value 0.04 for univariate and p-value 0.03 for multivariate analysis.

	Univariate		**Multivariate**	
	OR (95% CI), n = 91	*p*	OR (95% CI), n = 91	*p*
Lowest Tertile	Reference		Reference	
Intermediate Tertile	4.55 (1.38-15.05)	0.01	5.46 (1.55-19.20)	<0.01
Highest Tertile	1.51 (0.54-4.24)	0.4	1.25 (0.42-3.74)	0.7

Multivariate model: adjusted for age, gender and presence of psychotic symptoms
OR = odds ratio, CI = confidence interval

S100B and remission

As shown in Table 2, there is an overall difference between S100B tertiles (p = 0.03) with respect to remission rates. Patients in the intermediate tertile (S100B: 33 ng/L - 53 ng/L) have higher odds on remission compared with patients in the lower tertile: odds ratio (OR) 5.46 (95%Confidence Interval (CI): 1.55-19.20). Confidence intervals are wide as expected with a small sample size. Also, patients in the highest tertile (S100B: > 54 ng/L) tended to have a higher odd on remission as compared with the lowest tertile, although this was not significant: OR 1.25 (95%CI: 0.42-3.74). Presence of psychotic symptoms was identified as putative confounder and was therefore included as covariate in multivariable analysis. Pharmacotherapy resistance and BMI were also identified as putative confounders (p = 0.1 and p < 0.01). However, considering the number of missing values (respectively, n = 8 and n = 30) of both covariates, we decided to include only presence of psychotic symptoms in multivariable analyses, in order to maintain sufficient power. There was no significant multicollinearity between covariates. In separate post hoc analysis including pharmacotherapy resistance and BMI as covariates (n = 56), a higher odd on remission for patients in the middle tertile compared with the lower tertile was found, although not significant: OR 3.76 (95%CI: 0.67-21.11). In addition, post hoc analysis showed an association between higher BMI and higher levels of S100B, p for trend = 0.01. Post hoc analyses with inclusion of baseline S100B outliers (n = 3) did not alter our findings. To test the robustness of our findings, analyses were repeated for dichotomized values of S100B, cut-off median value (≥ 42 ng/L), however results did not reach significance: OR 1.82 (95%CI: 0.73-4.56).

S100B and time to remission

In both univariate and multivariable Cox regression analyses, patients in the intermediate tertile were more likely to remit from depression over time, compared with the lowest tertile: HR 1.96 (95%CI: 1.04-3.72). For the dichotomized value of S100B, the HR for remission was 1.45 (95%CI: 0.86-2.44).

S100B as a biomarker

When measuring the predictive values of S100B as a biomarker of treatment outcome a sensitivity of 55.7% and specificity of 60.0% was found. The positive predictive value was 73.9% with a false positive rate of 40.0%. The negative predictive value was 40.0% with a false negative rate of 44.3%.

No change in S100B between pre- and post-ECT measurement

As shown in Figure 1, there was no statistically significant difference in baseline and post-ECT S100B levels between remitters and nonremitters (respectively U = 813, p = 0.4 and U = 617.5, p = 0.2). In addition, there was no statistically significant difference in delta S100B from baseline to post-ECT between remitters and nonremitters (delta remitters = 1 ng/L, delta nonremitters = 2.5 ng/L, U = 723.5, p = 0.9). Median value for

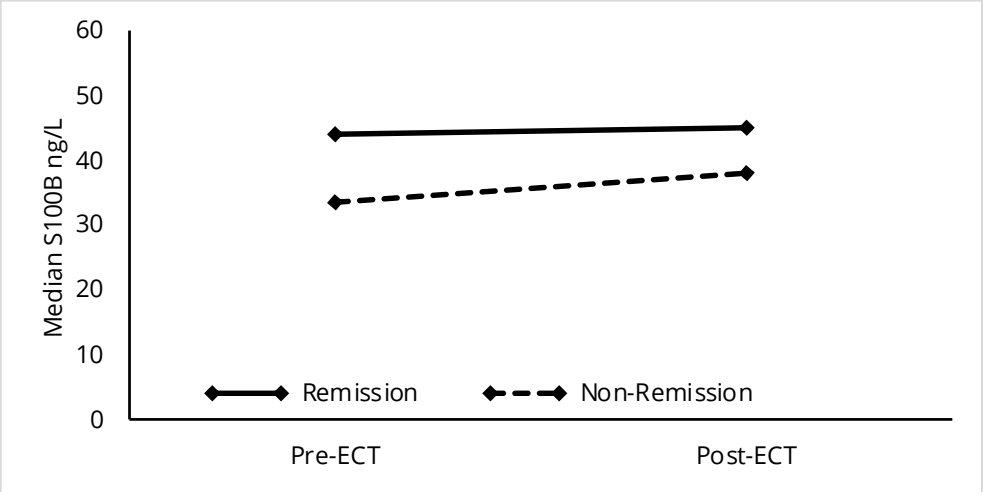

Figure 1. S100B levels at baseline and one week post-ECT between groups of remitters and non-remitters in older depressed patients treated with ECT (n = 91).

S100B in remitted patients was 44 ng/L at baseline and 45 ng/L post-ECT. Two patients were excluded from further analysis with a higher than three IQR increase in S100B, respectively a change of 618 ng/L and 457 ng/L.

No association with depression severity

There were no significant associations between baseline S100B and baseline MADRS (Spearman: -0.05, p = 0.6), recurrent depression (defined as at least one previous episode of depression, Spearman: 0.08, p = 0.4), presence of psychotic symptoms (Spearman: 0.12, p = 0.3) and duration of index episode of depression (Spearman: -0.09, p = 0.4).

DISCUSSION

The aim of this study is twofold. First, we aim to determine whether higher S100B is associated with remission of depression after treatment with ECT. Second, we aim to investigate whether S100B reflects a state marker of depression activity, by monitoring change in levels pre- and post-ECT and investigating the association of S100B with severity of depression. We therefore assess the glial protein S100B in depression in a large cohort of patients treated with ECT. Our study provides evidence that higher serum S100B levels are associated with favourable treatment outcome and faster remission in response to ECT and demonstrates similarity in S100B levels post-ECT compared with pre-ECT in those remitted from depression. These findings are contrary to the idea that S100B reflects a state marker of major depression.

Our findings confirm the association between serum S100B levels and responsiveness to treatment. A favourable treatment response to antidepressant medication or ECT in depressed patients with higher levels of baseline S100B was demonstrated in multiple, albeit small studies, summarized in Table 3.[14,15,17–19] All but one[16] study suggested increased responsiveness to treatment in patients with higher levels of S100B. These findings suggest the positive impact of S100B on plasticity processes. One hypothesis explaining these results might be that depressed patients suffer from a loss of neuroplasticity. The micro inflammation in the brain, initiated by neuronal impairment caused by depression[15] can result in a compensatory release of S100B, counteracting the neurodegenerative mechanisms of major depression. As suggested by Rajewska-Rager et al., S100B might have a positive impact on neuroplasticity processes[20] because of its neuroprotective effect by inducing neuronal growth and differentiation. This theory is supported by increasing evidence showing a decreased

Table 3. Overview of cohort studies examining baseline S100B and its relationship to depression treatment outcome or examining change in pre- and post-treatment levels of S100B.

	Treatment	n	Mean Age	Associated to treatment response	Mean baseline S100B (ng/L) Responders	Mean baseline S100B (ng/L) Non-responders	Change in S100B in responders
Schroeter et al. 2002	SSRI / TCA	9	44	n.d.	n.d.	n.d.	decrease[2]
Arolt et al., 2003	SSRI / TCA	25	46	yes	1511	721	n.d.
Jang et al., 2008	SSRI / SNRI / TCA	59	60	yes	69	57	=
Ambrée et al., 2015	SNRI / TCA	40	52	yes	63	41	=
Arts et al., 2006	ECT	12	54	yes	n.a.	n.a.	n.d.
Kranaster et al., 2014	ECT	19	66	no	52	59	n.d.
Maier et al., 2018	ECT	11	47	yes	70	50	=
Carlier et al., 2019	ECT	91	73	yes	44	34	=

[1] measured in heparin-plasma, therefore values might deviate

[2] all patients responded to treatment, therefore no comparison was made with nonresponders

n.a. no data available

n.d. not determined

density in glial cells in mood disorders suggesting a disruption in neuroplasticity as etiological factor.[33–35] In our study, patients in the highest S100B tertile did not have a significantly better treatment response compared with the lowest tertile. Although patient samples were within the nanomolar range, this may be due to the wide distribution of S100B in the highest tertile, as a result of heterogeneity within this subsample of patients, and some patients having higher levels of S100B as a result of other factors than depression, such as an acute phase reaction.[11] The sensitivity and specificity of S100B were low suggesting this marker is not eligible as a sole predictor of treatment outcome. The additional benefit of combining biomarkers is subject for further research.

Second, there is an ongoing discussion whether higher levels of S100B in patients with depression represent a state marker of illness activity as S100B levels are consistently found elevated in depressed patients compared with healthy controls.[6,7,20] If S100B were a state marker of depression, its levels would be expected to decrease after remission of depression and to be associated with severity of depression. However, our study, in line with one small ECT study (n = 11), shows there is no change in S100B over the course of ECT in both remitters and nonremitters, see also Table 3. In addition, in our study, with a larger study sample, S100B is not associated to depression severity. Two other studies describe no change in S100B after treatment with antidepressant medication[17,18] compared with one study showing reduced S100B levels after antidepressant treatment.[36] Previous findings are inconsistent on whether S100B levels are influenced by severity of symptoms[15,17,36,37] or not.[16,18] The majority of studies found no correlation between depressive symptoms and S100B.[6]

Our findings contradict the idea that S100B is a state marker of illness activity and fuel the idea that higher levels of S100B are a long-term adaptation of the brain to stress associated with depression or is innate contributing to the onset of depression. A positive correlation between levels of S100B and stressful activity has been shown in physicians on duty as well as in mother and new-born after prolonged labour[11,38,39] establishing the capacity of the brain to adapt, in this case to stressful circumstances. In addition, exposure to childhood trauma has been associated to higher levels of S100B in adolescents.[40] If this hypothesis is confirmed, this brain adaptation could on the one hand inflict susceptibility for psychiatric disease as is underlined by lower S100B in healthy compared with depressed patients.[6,31] On the other hand, this adaptation could imply an impact on neuroplasticity processes as mentioned above. Additional support for this hypothesis is the fact that an increase

of S100B is not selectively found in depression but is also found in patients with schizophrenia.[41,42] In addition, two studies found evidence that increased S100B levels help to restore normal cognitive functioning in depressed patients[43,44], strengthening the idea that either S100B, or S100B releasing glial cells, have the ability to restore impaired processes. It would be interesting to look at cognition in relation to S100B in future studies.

Finally, it should be mentioned that S100B can exert a neurotoxic function as opposed to the neurotrophic function described above. Increased serum levels of S100B have been attributed to increased permeability through an impaired blood brain barrier (BBB) and is used as a biomarker of brain injury in Neurology.[11,13] However, recent evidence suggests that higher serum S100B levels imply an active S100B release from glial cells reflecting neuroplasticity and glial activation rather than release from damaged astrocytes[45] and should be interpreted as normal passage of S100B to the extracellular fluid.[13,45,46] Studies in schizophrenia patients support this notion, as increased serum levels of S100B coincided with increased glial activation as detected by MR-spectroscopy.[47] Because the biologic effects of S100B are thought to be dose-dependent, the increased concentrations observed in our sample could indicate neuronal activation rather than neuronal damage or BBB damage.

Strengths and limitations

Notably, our findings should be interpreted in the context of the following strengths and limitations. To our knowledge, the current study has the largest sample of serum S100B in depressed patients referred for ECT. Nonetheless, confidence intervals are wide. Any conclusions drawn from these results need to be replicated in a larger sample size. Second, the substantial set of clinical data collected from patients allows us to adjust for putative confounders. An additional strength is that our study includes a well described, rather homogenous sample of severely depressed patients. On the other hand, a limitation of this study is that results might not be applicable to younger patients with mild or moderate depression. It is shown previously that age may have impact on S100B[7,] therefore age is controlled for in our analyses. In addition, besides brain injury and glial activation, there are several other factors known to increase S100B, including heart ischemia, melanomas, BMI and the use of serotonergic medication.[9,11,32,48] Adjustment for ischemic heart diseases, presence of malignancies and the use of antidepressant medication during ECT does not alter our results making it less likely to have influenced S100B levels in our sample. In addition, S100B levels were determined one week after ECT, therefore it is unlikely that treatment received after discontinuing ECT

(maintenance ECT or antidepressant medication) has influenced our results. Next, post hoc analysis shows a significant upward trend in BMI for higher S100B levels. This finding is explained by the well-known association between adipose tissue and levels of S100B.[48,49] Despite the missing data on BMI, post hoc analysis with the available data (n = 56) showed similar results, which suggests a limited effect of BMI on the association between S100B and ECT outcome. In line with this, as S100B is viewed as a biomarker of brain injury[13], one might suspect that ECT-induced seizures cause an increase in levels of S100B, limiting any statements on the change scores between pre- and post-ECT S100B. However, several studies have shown that there is no increase in S100B during the course of ECT and found no association between S100B and energy dose or seizure duration[16,50,51], suggesting ECT does not cause brain injury and thus does not cause an increase in levels of S100B. Finally, Yang et al. have shown a positive correlation between levels of S100B and number of episodes of depression which might suggest a form of kindling as the brain is going through recurrent depressive episodes.[31] Therefore, one might expect to find higher S100B levels in patients with more previous episodes or a longer duration of index episode of depression. The absence of information on the number of previous episodes is considered a limitation in this respect. In addition, no correlation is found between S100B and index episode duration. However, the relative long index episode duration of the entire sample (mean: six months), might explain the absence of this correlation. Future studies should include the number of previous episodes and should include both short and long index episode duration.

Future implications

Higher levels of S100B are associated with favourable treatment outcome. Conversely, patients with low levels of S100B tend to benefit less from both ECT and antidepressant medication. Therefore, further research is needed to unravel treatment strategies for these patients. Although not yet studied in depression, a handful of studies regarding the effect of S100B on neurogenesis find positive neuroprotective effects of daily S100B administration in mice or human cell lines.[52–54] Given our findings, increasing the level of S100B may contribute to responsiveness to treatment.

Conclusion

This study provides evidence that higher levels of S100B in patients with severe depression, treated with ECT, are associated with higher and faster remission rates. Serum S100B levels do not decrease upon remission, which makes it less likely

that S100B is a state marker for depression. Our findings warrant replication. If future studies confirm our findings, higher levels of S100B could, in combination with other putative markers, potentially identify a subgroup of patients with favourable ECT outcome.

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SUPPLEMENTAL MATERIAL

There is no clear definition of treatment resistance. In our paper, the definition of Prudic et al. (1996) was used, who have classified medication resistant as at least one antidepressant trial of any type with an adequate dose for a minimum of 4 weeks.[1] In a review of Berlim et al. (2007) another definition is recommended, that is, at least two antidepressant trials with adequate dose and duration.[2] The distribution of patients with medication resistance using the definition of both Prudic et al. and Berlim et al. are shown in the table below.

The number of patients that fall into the medication resistant category is reduced by 50 percent when using the definition of Berlim et al., however, results from post hoc regression analyses are minimally altered.

Supplemental Table. Distribution of treatment resistance using two different criteria in older depressed patients treated with ECT.

	Total	**Lowest Tertile**	**Intermediate Tertile**	**Highest Tertile**	***p***
Characteristic					
- Medication resistant 1 trial, No. (%)	56 (67.5)	14 (53.8)	21 (67.7)	21 (80.8)	0.1
- Medication resistant 2 trials, No (%)	27 (32.5)	7 (26.9)	11 (35.5)	9 (34.6)	0.8

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CHAPTER 3

INFLAMMATION AND REMISSION IN OLDER PATIENTS WITH DEPRESSION TREATED WITH ELECTROCONVULSIVE THERAPY

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ABSTRACT

Background

Compelling evidence links elevated C-reactive protein (CRP) and other inflammatory markers to poor treatment outcome to antidepressant medication. Little is known about the contribution of low-grade inflammation on treatment response to Electroconvulsive Therapy (ECT) in severely depressed patients.

Method

Associations between serum levels of CRP, Interleukin-6, Interleukin-10, Tumour Necrosis Factor-α, and remission of depression, time to remission and speed of decline of depressive symptoms, were examined in 95 older (mean age: 73.1) depressed patients treated with ECT.

Results

Moderately elevated levels of CRP at baseline (3 to 10 mg/L), but no other inflammatory markers were associated with higher remission rates. Odds ratio for remission, in those with moderately elevated CRP levels was 3.62 (95% confidence interval [CI],1.09-11.97; p = 0.04). Time to remission was shorter in those with moderately elevated CRP levels, p=0.05. Speed of decline was higher in those patients with moderately elevated CRP levels as compared to those with low CRP levels (decline of 3.2 MADRS points per administration vs. 2.3 points per administration, p=0.03). Limitations: because of the observational design, residual confounding through other lifestyle- or demographic factors cannot be ruled out.

Conclusions

Whereas earlier studies show that low-grade inflammation contributes to poor treatment response in those treated with antidepressants, our study provides clues that low-grade inflammation does not have such a detrimental effect on the treatment response to ECT. This is underscored by our finding that moderately elevated CRP levels were associated with increased remission rates in depressed patients treated with ECT. Replication studies are warranted.

INTRODUCTION

Compelling evidence linking depression to systemic inflammation has emerged over the last twenty years. Administration of bacterial endotoxin, inducing an inflammatory cytokine response in animals and humans, reproduces depression-like "sickness behaviour", such as decreased interest, social withdrawal, insomnia, decreased motor activity and anorexia.[1–3] Recent meta-analyses of cross-sectional studies showed that elevated levels of inflammatory markers in patients, such as interleukin 6 (IL-6) and C-reactive protein (CRP) are associated with depression.[4–7] Moreover, results from longitudinal studies suggest a causal relationship between elevated levels of inflammatory markers and incident depressive symptoms[8–10,] although controversy regarding the role and contribution of inflammatory markers on depression still exists.[7,11,12]

The controversies on the role of inflammatory markers on depression are possibly due to differences in the patient samples under study. It is likely that inflammation is not generally present in depression but linked to an "inflammatory depression subtype". Several studies repeatedly reported that elevated levels of inflammatory markers are associated with later age of onset, comorbid physical illnesses, cognitive impairment, reduced motivation, recurrent episodes, and persistence of symptoms.[13–18] In addition, results from meta-analysis suggested that patients with elevated inflammatory markers had more non-response to antidepressant medication.[15] It is possible that this subgroup of patients with elevated levels of inflammatory markers might profit from anti-inflammatory medication as is proposed by Lang[19] and Miller.[20]

Among the treatments for depression, electroconvulsive therapy (ECT) is superior effective compared with antidepressant medication[21], with remission rates ranging between 48% and 65% in those with medication-resistant depression.[22,23] Several reviews examined inflammatory markers through the course of ECT. They suggest an acute immune response after a single ECT administration followed by a decrease in cytokines levels after multiple ECT administrations.[24–29] One study has examined the predictive effect of inflammatory markers on ECT response in depressed patients. Findings from this study showed that elevated CRP levels were associated with a reduction of depressive symptoms in women (n=15). These findings, although obtained in a study with limited group size, fuel the controversy over the role of inflammatory markers on depression.[30]

We studied the effect of ECT on remission, time to remission and speed of decline of depressive symptoms in a population of depressed patients with low-grade inflammation. Based on previous findings[13,15,17], we hypothesize that moderately elevated levels of inflammatory markers contribute to poor treatment outcome, not only in those treated with antidepressant medication but also in those treated with ECT.

METHODS

Study sample

This study was conducted as part of the Mood Disorders in Elderly treated with Electroconvulsive Therapy (MODECT)[31], a naturalistic longitudinal cohort study (n=110) of patients aged 55 years and older with severe unipolar depression. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving patients were approved centrally by the Ethical Review Board of the Amsterdam University Medical Centre, and subsequently by the ethical review board of the Leuven University Hospital. Written informed consent was obtained from all patients. Patients received ECT treatment from two tertiary psychiatric hospitals in the Netherlands (GGZ inGeest, Amsterdam) and Belgium (University Psychiatric Centre, KU Leuven) and were recruited between 1 January 2011 and 31 December 2013. Patients with a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnosis other than unipolar depressive disorder were excluded. Also, patients with a major neurological illness, including Parkinson disease, stroke, and dementia, were excluded. Fifteen subjects were excluded from the analysis, due to missing data regarding biomarkers or Montgomery Åsberg Depression Rating Scale (MADRS) scores.[32] Age, sex, age of onset of depression, baseline MADRS score and the total number of ECT treatments were not associated with attrition.

Measurements

Diagnosis of major depressive disorder, according to the DSM-IV, was made by a psychiatrist and validated with the MINI International Neuropsychiatric Interview (MINI).[33,34] The severity of depression was assessed using the MADRS one week before and one week post-ECT treatment. For clinical relevance of study results, primary outcome measures were remission, defined as a MADRS score of less than ten at two consecutive ratings, and time to remission.[35] We also determined speed of decline of depressive symptoms, defined by reduction of MADRS score relative to the number of

ECT administrations. Serum samples were collected one week prior to ECT between 07h30 and 09h30 and were stored at -85 °C. Samples were assayed between seven and 43 months after collection. Number of chronic somatic diseases, including cardiovascular disease, hypertension, diabetes mellitus, chronic respiratory disease and arthrosis, was assessed in a semi-structured interview. Medication-resistance was defined as a history of at least one antidepressant trial with a resistance score higher or equal to three according to the Antidepressant Treatment History Form (ATHF).[36] A trial's strength on the ATHF is rated from one, duration shorter than four weeks, to five, duration longer or equal to four weeks with adequate antidepressant dose and lithium augmentation. Depression characteristics were defined as medication-resistant, early-onset of depression (first episode before 55 years of age), duration of index episode or presence of psychotic symptoms (based on the DSM-IV and MINI).[33,34] We regarded several variables as potential confounders, including socio-demographic variables (sex and age), total number of chronic disease, Body Mass Index (BMI), current smoking (yes/no), alcohol use (yes/no), and depression characteristics (medication resistance, early onset, duration of index episode and presence of psychotic symptoms).

Inflammatory markers

Serum levels of Interleukin-6 (IL-6), Interleukin-10 (IL-10) and Tumour Necrosis Factor-α (TNF-α) were simultaneously determined with a 3-step multiplex digital immunoassay, the Simoa Human Cytokine 3-Plex A assay kit (Quanterix; cat.# 101160), using the Simoa HD-1 Analyzer and Single Molecule Array (Simoa) technology. Intraassay and interassay reproducibility (coefficient of variation (CV), for interassay cv based on data from ten runs) were 4.3% and 5.9% for IL-6, 3,9% and 5.3% for IL-10 and 4,2% and 5.3% for TNF-α, respectively. Upon thawing, the serum samples were mixed by inverting, spun at 4 °C (10'; 10000g), and assayed immediately. As a quality control, samples containing either low or high cytokine levels, were included in each plate run. Low grade inflammation was defined as levels of inflammatory cytokines above the median. Levels of CRP were determined with the High Sensitive (CRPhs) kit (Cobas CRPHA; Cat. No. 04628918 190) using the Cobas 6000 module c501 (Roche Diagnostics), which measures complexes between CRP in the sample and specific antibodies coupled to latex particles. The measurement range of the assay is 0.15 – 20 mg/L (after rerun (diluted sample) up to 300 mg/L). Two control samples were included in each run. Cytokine and CRP determinations were performed at the Clinical Chemistry department of Amsterdam UMC, Vrije Universiteit Amsterdam. Low grade inflammation for CRP, that is, moderately elevated CRP (cut-off: 3mg/L), was defined in accordance with clinical guidelines from the Centres for Disease Control and Prevention and the American Heart Association.[37,38]

CRP values higher than 10 mg/L were excluded from analyses (n=10) to avoid possible confounding effects of systemic inflammatory diseases and acute infection.[37]

ECT procedure

Patients received twice-weekly ECT in accordance with the Dutch guideline for ECT.[39] All treatments were administered with the Thymatron System IV (Somatics, LLC, Lake Bluff, IL, USA) (maximum energy 200%, 1,008 C). The stimulus intensity was determined by empirical dose titration; initial seizure threshold x6 for right unilateral ECT and x2.5 for bilateral ECT. All patients were treated with brief-pulse ECT (1.0 ms). A course started with right unilateral ECT preferably, when clinical condition worsened (i.e. an increase in total MADRS scores, presence of debilitating psychotic symptoms, increased suicidality, dehydration or weight loss, or when after six unilateral treatments there was no clinical improvement according to the judgement of the treating psychiatrist), treatment switched to bilateral lead placement. ECT was continued until remission or discontinued when patients showed no further improvement in clinical condition during two weeks after a minimum of six unilateral and six bilateral ECT administrations. Psychotropic medication was discontinued at least one week before ECT or kept stable before ECT and during the ECT course if necessary.

Statistical analyses

IBM SPSS statistics 23 was used for all data analyses. Differences in covariates between remitters and non-remitters were tested using Chi-square statistics for categorical variables. For continuous variables with a normal distribution, independent t-tests were performed. Non-parametric testing was applied for non-normally distributed variables. All values of inflammatory markers were skewed to the right, and natural log transformed. For clinical purposes all analyses were performed using both continuous and dichotomized values of inflammatory markers. Outliers were determined using 1.5x IQR after log transformation and were excluded from analyses (n=1, TNF-α). The relation between levels of inflammatory markers and remission was assessed using binomial logistic regression analyses. No adjustment for multiple testing was made since hypotheses were formed on the relation between inflammatory markers and remission of depression. A Cox proportional hazards model for time-to-event was used to evaluate the association between inflammatory markers and time (number of ECT administrations needed) to remission. Variables in model 1 were obtained using univariate analyses. Consecutively, in model 2, the following covariates; age, sex, baseline MADRS, depression characteristics, number of chronic disease, BMI, smoking and alcohol use, were eliminated one by one according to the level of non-significance

(backward regression analysis) and included in the model if sustained significant. Additionally, multicollinearity was tested using variance inflation factor. We used linear regression to determine the effect of CRP levels on speed of decline of depression symptoms, adjusted for the above-mentioned covariates. IL-6 and TNF-α values were summed up after conversion to a z-score to evaluate if a total sum score had additional predictive power (inflammation composite). Regression coefficients in the logistic and Cox models were evaluated with a two-sided Wald test. Cohen's d statistic was used to calculate effect sizes.[40] Finally, in all multivariable analyses we added age and sex as potential confounders.

RESULTS

The mean age of patients was 73.1 years (range 55-92 years). The mean baseline MADRS score of the sample was 33.7, indicating severe depression. 65 of 97 (67.7%) of patients were identified as remitters. The mean number of ECT treatments was 11.6.

Table 1. Demographic and clinical characteristics in depressed patients treated with ECT

	Total	**Remission**	**No remission**	**T/X/U(df), *p***
	n = 95	n = 65	n = 30	
Socio-demographics				
Age, years, mean (SD)	73.1 (8.2)	73.2 (8.2)	72.8 (8.3)	-0.19(93), 0.8
Women, No. (%)	65 (68.4)	42 (64.4)	23 (76.7)	1.4(1), 0.2
Level of education, years, median (IQR), n=83	9.0 (3.0)	9.0 (3.0)	9.0 (6.8)	702, 0.8
Baseline MADRS, mean (SD)	33.7 (9.1)	33.4 (8.6)	34.4 (10.2)	0.5(93), 0.6
MADRS post-ECT, median (IQR)	6.0 (9.0)	4.0 (4.5)	18.5 (14.8)	<0.1, <0.01
ECT sessions, median (IQR)	11.0 (6.0)	10.0 (4.0)	14.0 (5.3)	561, <0.01
Smoking, No. (%)	28 (35.4)	21 (38.9)	7 (28)	0.9(1), 0.3
BMI, mean (SD), n=55	23.0 (3.9)	23.1 (4.0)	23.0 (3.8)	0.33(53), 0.9

SD = standard deviation, IQR = interquartile range, No. = number, MADRS = Montgomery Åsberg Depression Rating Scale, BMI = body mass index

Table 1. Continued

	Total n = 95	**Remission** n = 65	**No remission** n = 30	**T/X/U(df), *p***
Psychotropic medication use				
Antidepressant use, No. (%)	13 (13.7)	8 (12.3)	5 (16.7)	0.3(1), 0.5
Antipsychotic use, No. (%)	7 (7.4)	6 (9.2)	1 (3.3)	1.1(1), 0.3
Somatic morbidity				
Cardiovascular disease (CVD), No. (%)	22 (23.7)	12 (19.0)	10 (33.3)	2.3(1), 0.1
Hypertension, No. (%)	27 (29.0)	20 (31.7)	7 (23.3)	0.7(1), 0.4
Type 2 diabetes, No. (%)	8 (8.6)	5 (7.9)	3 (10)	0.1(1), 0.7
No. of chronic diseases [1]	1 (2)	1 (2)	1 (1)	890, 0.6
Depression characteristic				
Psychotic No. (%)	44 (46.3)	34 (52.3)	10 (33.3)	3.0(1), 0.1
Medication resistant, No. (%), n = 87	60 (69.0)	37 (61.7)	23 (85.2)	4.8(1), 0.03
Early onset, No. (%)	41 (43.2)	25 (38.5)	16 (53.3)	1.9(1), 0.1
Index episode, months, median (IQR)	6.0 (10.0)	5.0 (6.0)	8.0 (12.5)	509, <0.01
Markers, median (IQR) [2]				
CRP (mg/L, n=85)	1.4 (3.3)	2.3 (3.9)	1.0 (1.8)	505, 0.01
IL-6 (pg/ml)	2.8 (4)	3.0 (4.6)	2.4 (2.8)	829, 0.2
IL-10 (pg/ml)	0.9 (0.6)	0.9 (0.6)	0.9 (0.7)	882, 0.5
TNF-α (pg/ml)	4.3 (2.2)	4.2 (2.3)	4.4 (2.2)	960, 0.99

[1] Chronic disease is defined as the total number of chronic diseases, including cara, CVD, hypertension, type 2 diabetes mellitus, arthroses/rheumatoid disorders

[2] Marker values before log transformation

IQR = interquartile range, No. = number, CVD= cardiovascular disease, HT = hypertension, DM = diabetes mellitus, CRP = C-reactive protein, IL-6 = interleukin-6, IL-10 = interleukin-10, TNF-α = tumour necrosis factor–α

Differences in clinical characteristics are shown in Table 1. CRP levels were significantly higher at baseline in remitters compared to non-remitters, see Table 1.

Low-grade inflammation and remission

Univariate logistic regression analysis showed that moderately elevated levels (3 to 10mg/L) of CRP at baseline were associated with higher remission rates of depression post-ECT, OR: 3.31 (95% confidence interval [CI]: 1.10-9.97). In those with CRP of 3 or higher, remission was 83.9%, whereas remission was 61.1% in those with CRP levels lower than 3, OR: 3.62 (95% CI: 1.09-11.97). Other markers of inflammation, including dichotomized values of IL-6, IL-10, and TNF-α, were not significantly associated with remission of depression post-ECT (Table 2). Next, we examined low-grade inflammation and ECT outcome in multivariable regression analyses. Variance inflation factors were <2.0 indicating no multicollinearity. Model 2 is adjusted for age, sex and medication-resistance. When all covariates were added in a model, moderately elevated CRP levels remained a significant predictor of remission of

Table 2. Univariate and multivariate logistic regression analyses in depressed patients treated with ECT (n = 95)

	Univariate, Model 1	**Multivariate,** Model 2 [3]
	OR (95% CI)	OR (95% CI)
CRP, continuous [1]	2.57 (1.19-5.57)	3.16 (1.30-7.70)
Low CRP (≤ 3 mg/L) vs. moderately elevated CRP (3 to 10 mg/L) [1]	3.31 (1.10-9.97)	3.62 (1.09-11.97)
IL-6	1.35 (0.81-2.23)	1.95 (0.93-4.10)
IL-10	1.47 (0.58-3.73)	1.87 (0.54-6.45)
TNF-α [2]	1.20 (0.38-3.83)	1.40 (0.32-6.07)
Inflammation Composite	1.23 (0.80-1.90)	1.71 (0.81-3.62)

[1] Number of patients with complete CRP is 85

[2] Number of patients with complete TNF-α is 94

[3] Model 2 adjusted for medication resistance, age, and gender after backward step-wise regression

CRP = C-reactive protein, IL-6 = interleukin-6, IL-10 = interleukin-10, TNF-α = tumour necrosis factor–α, inflammation composite = IL-6 and TNF-α, OR = odds ratio, CI = confidence interval

depression. Post hoc analysis for the effect of CRP on remission were done, adjusting for BMI, since it is known that BMI has a substantial impact on both inflammation and depression. This was done despite the fact that there was no difference in BMI between patients with low or moderately elevated levels of CRP. Findings from our post hoc regression analyses did not alter the effect of moderately elevated CRP levels on remission (data available in supplemental material). Additionally, in post hoc analyses, no significant associations were found between baseline levels of inflammatory markers and use of psychotropic medication (data available in supplemental material). Cohen's effect size value for CRP suggested a moderate impact of CRP on remission (d=0.42). The inflammation composite of IL-6 and TNF-α in a z-score, was not a predictor of ECT outcome, OR: 1.71 (95% CI:0.81-3.61).

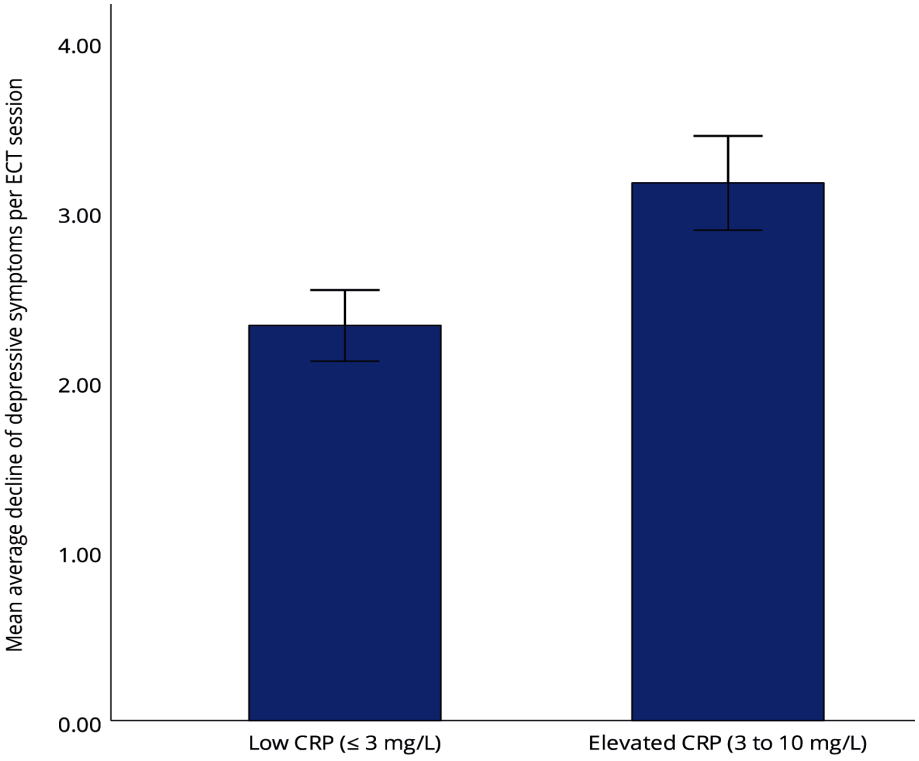

Figure 1. Contribution of low and elevated CRP levels to the speed of decline in MADRS points, per ECT administration in depressed patients

Table 3. Univariate and multivariate Cox proportional hazard analyses in depressed patients treated with ECT (n = 95)

	Univariate, Model 1 HR (95% CI)	**Multivariate**, Model 2 [3] HR (95% CI)
CRP, continuous [1]	1.39 (0.97 to 1.99)	1.43 (0.99 to 2.07)
Low CRP (≤ 3 mg/L) vs. moderately elevated CRP (3 to 10 mg/L) [1]	1.53 (0.91 to 2.55)	1.64 (0.96 to 2.80)
IL-6	1.08 (0.82 to 1.42)	1.11 (0.83 to 1.48)
IL-10	1.24 (0.75 to 2.04)	1.25 (0.76 to 2.07)
TNF-α [2]	1.13 (0.61 to 2.12)	1.14 (0.61 to 2.13)
Inflammation Composite	1.08 (0.93 to 1.24)	1.07 (0.93 to 1.23)

1 Number of patients with complete CRP is 85
2 Number of patients with complete TNF-α is 94
3 Model 2 adjusted for age and gender after backward stepwise regression
CRP = C-reactive protein, IL-6 = interleukin-6, IL-10 = interleukin-10, TNF-α = tumour necrosis factor–α, inflammation composite = IL-6 and TNF-α, HR = hazard ratio, CI = confidence interval

Inflammation and speed of decline of depressive symptoms

Using linear regression we examined the association between inflammatory markers and the speed of decline (defined as reduction of MADRS score relative to the number of ECT administrations) adjusted for all covariates using backwards stepwise regression. Baseline MADRS contributed significantly to the model fit. The analysis showed that with each natural logarithm unit increase of CRP there was a decline of 0.73 MADRS points per ECT administration (ß 0.73 (95% CI: 0.14-1.33) adjusted for age, sex, and baseline MADRS, with an R^2 of 0.2. This result remained similar when we compared those with moderately elevated CRP levels (3 to 10 mg/L) to those with lower CRP levels, that is, there was an estimated decline of 3.2 MADRS points per administration in those with moderately elevated CRP levels vs. 2.3 points per administration in those with lower CRP (ß 0.97 (95% CI: 0.12-1.82), see Figure 1. We found no effect of other inflammatory markers on speed of decline of depressive symptoms,data not shown. Table 3 presents both unadjusted and adjusted results from the Cox regression model. The hazard ratio (HR) for remission per unit

increase of CRP was 1.4 (95% CI, 0.99-2.07). All other inflammatory markers were not associated with speed of remission, Table 3. In Cox regression analyses, none of the covariates was associated with depressive symptoms.

DISCUSSION

Our finding that moderately elevated CRP levels (3 to 10 mg/L) at baseline are associated with increased remission rate, improved time to remission and increased speed of decline of depressive symptoms in depressed patients treated with ECT was contrary to our primary hypothesis, i.e. moderately elevated CRP levels would contribute to poor treatment response. Our hypothesis was based on meta-analyses on the role of inflammatory markers in patients treated with antidepressant medication and on findings from observational studies.[13,15,17] Additionally, no consistent associations were found between other markers of low-grade inflammation, i.e. inflammatory cytokines, including IL-6, IL-10, and TNF-α, and ECT response.

Inflammation and depression

Our study shows that depressed patients with moderately elevated CRP levels, treated with ECT had superior outcome with higher remission rates and a greater reduction of depressive symptoms compared to those with low CRP levels. Our findings are strengthened by a preliminary study in which elevated CRP levels at baseline were associated with a lower end-of-treatment MADRS score, although the effect was only observed in women (n=15/29), not in men.[30] Additionally, there was no association between CRP and remission, the hallmark of effective treatment of depression, likely because the remission rate of this study was relatively low (34%; n=10/29). In addition to CRP, Kruse et al. also observed an association with IL-6 and a post-ECT decrease in depressive symptoms. Although we found a similar contribution of CRP, we did not find an association of any outcome measure, including remission or speed of decline of depressive symptoms as a result of ECT, with baseline levels of IL-6 and other cytokines (TNF-α and IL-10). This difference between cytokines and CRP may be due to different kinetics for CRP and cytokine levels.[41–43] CRP levels remain elevated over a prolonged period, when there is chronic stress, whereas subsequent decline to baseline for cytokines is much faster.[41–43] Since the majority of our patients were depressed for several months, before the start of ECT, this could explain why we did not find an association between cytokines but did find an association with CRP.[41–43]

Possible explanations

Several hypotheses can explain the findings from our study such as (i) patients eligible for ECT have different characteristics compared to depressed patients in studies on antidepressant medication and (ii) ECT has a different working mechanism. In our view the latter explanation, i.e. ECT has a different working mechanism compared to antidepressants, is the most plausible in explaining the effects of CRP on remission in our study. This view is based on the finding that non-response to antidepressants is associated with overall activation of the inflammatory system[13,15,17,18,44], and the finding from a randomized controlled trial that treatment with anti-inflammatory drugs in patients with elevated CRP contributed to higher treatment response.[45] Although a single ECT administration results in an immediate and transient increase of cytokine levels as result of an acute immune response[25,28,46], multiple ECT administrations eventually result in normalization and long-term down-regulation of cytokine levels.[24,47–49] In other words, ECT has an overall anti-inflammatory effect after a full ECT course, contributing to remission. This idea that anti-inflammatory aspects of ECT are relevant is further strengthened by three meta-analysis[50–52] that demonstrated that anti-inflammatory treatments have a beneficial effect on depressive symptoms in patients with depressive symptoms. In addition, Vinberg et al. have found promising effects of anti-inflammatory treatment with erythropoietin in those patients with high levels of CRP.[53] Van Buel et al. proposed a direct role of ECT on inflammation through reinforcement of neurotrophin expression, that in turn, can induce neurogenesis and have antidepressant effects, as was observed in animal studies.[28] Microglia, and innate immunity in general, are indispensable for central nervous system (CNS) plasticity and expression of neuroprotective neurotrophins, including Brain Derived Neurotrophic Factor. Van Buel *et al.* propose that chronic inflammation, which is common in patients with antidepressant-resistant depression and somatic comorbidity[18], can bring microglia, the immune regulatory cells in the brain, into a state of prolonged suppression. Activation of the peripheral innate immune system could stimulate the microglia to resume their repair and antidepressant capacities in the CNS. Likewise, ECT may initiate microglia to produce neurotrophic factors, followed by an overall anti-inflammatory effect, which both may contribute to the increased remission rates observed in our study. The remission of depression ranges between 48% and 65% in those who fail to respond to antidepressant medication.[23-26] It could imply that ECT could be beneficial in those patients with low grade inflammation who fail to respond to antidepressant medication.[28]

As mentioned earlier, another explanation could be that patients eligible for ECT have different characteristics than those in studies on antidepressant treatment. It has

previously been suggested that low-grade inflammation is associated with depression severity and subtype of depression.[54,55] However, these studies are more often outpatient studies, or these findings are based on population-based studies. In general, patients eligible for ECT often have the highest severity scores of depression. In our study, adjustment for depression scores at baseline was a relevant covariate, since adjustment for MADRS score at baseline, further strengthened the association between moderately elevated CRP levels and speed of decline of depressive symptoms. Secondly, patients eligible for ECT have a shorter index episode of depression.[56] Patients in our population had an index episode of six months, whereas, the index episode is significantly longer when antidepressant medication is used, i.e. more than one year.[57] However, adjustment for index episode in our study did not alter our results. We were not able, in this study, to compare the association between inflammatory markers and a longer index episode, as described in STAR*D[57] for example. We here present novel findings that suggest that there is a group of clinical patients with moderately elevated CRP levels, in whom antidepressant medication has no effect, who do remit when treated with ECT. Additional research is needed to confirm these possible mechanisms.

Strengths and weaknesses

The current study has several strengths. First, due to its sample size we were able to show that moderately elevated CRP levels are not only associated with a reduction in depressive symptoms[30], we also showed that moderately elevated CRP levels were clinically relevant since they contributed to a significantly higher remission rate. Second the diagnosis of major depressive disorder with or without psychotic symptoms, according to the DSM-IV, was made by a psychiatrist and validated with the MINI International Neuropsychiatric Interview (MINI).[33] Third, one could argue that the validity of our findings is underscored by the coherence and consistency in our finding when using logistic, Cox and linear regression. All statistical tests were planned and hypothesis driven, therefore no adjustment for multiple testing were made. Additionally, our study is one of the few studies to determine the effect of CRP in a group of patients with the highest depression scores and a relatively short index episode of depression before ECT started.

In contrast, a limitation is that the sample exists of clinical, older (>55 years) patients, making these results not applicable to outpatients and to younger populations. Therefore, findings have to be replicated in severely depressed, younger outpatients with a relatively short index episode. It is important to note that our inflammatory

markers were measured on a single time point. This is a possible weakness of our study since it is unknown whether a single time point measure is sufficient to determine outcome of treatment, when inflammatory cytokines are used. On the other hand, there is ample evidence that a single time point measurement of CRP is a strong predictor for outcome of many disorders.[37,58–60] Moreover findings from Browning et al. suggest "that use of some inflammatory markers, such as CRP, with large within-individual variability, will underestimate the relationship between inflammation and disease, and thus relationships between inflammation and chronic disease may be stronger than previously appreciated".[61] This makes it less likely that single time point measures have influenced our results. Furthermore, our findings are based on administration of ECT twice weekly and are thus not applicable to administration thrice weekly, although studies show no difference in efficacy between twice or thrice weekly ECT.[62] In addition, we cannot compare differences in index episode and inflammatory markers between patients using antidepressants and patients in our study who received ECT, since we only have data on cytokines, CRP and patients treated with ECT, as described earlier in the discussion. Additionally, because the effect of psychotropic medication on inflammatory markers is relatively unknown[63], we cannot rule out the possibility that the use of psychotropic medication has influenced baseline levels of CRP and cytokines. However, post hoc analysis showed no significant associations between the two making it less likely to have influenced our findings. Also, the lack of information on concurrent use of anti-inflammatory medication limits our findings. To further explore whether ECT may have anti-inflammatory properties, future studies should include measurements of inflammatory markers post-ECT. Finally, we were able to adjust for a large number of putative confounders. Nonetheless, this is an observational study without control group, therefore, residual confounding through other lifestyle- or demographic factors cannot be ruled out.

Implications

ECT seems to be more effective in depressed patients with moderately elevated CRP levels (3 to 10 mg/L), Our finding is contrary to the idea that CRP levels contribute to poor treatment outcome in depression and warrant replication.[13,15,17] One could argue that ECT should be the first choice in those patients with moderately elevated CRP levels and severe depression. Proof for the effectiveness of such a personalized health strategy can only come from randomized clinical trials, comparing ECT and antidepressant medication, in those with severe depression and moderately elevated CRP levels.

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Univariate and multivariate logistic regression analyses in depressed patients treated with ECT

	Multivariate	
	Model 2[1]	Model 3[2]
	OR (95% CI)	OR (95% CI)
CRP	3.16 (1.30 to 7.70)	8.85 (1.54 to 51.01)[3]
IL-6	1.95 (0.93 to 4.10)	2.67 (0.80 to 8.98)
IL-10	1.87 (0.54 to 6.45)	1.17 (0.22 to 6.13)
TNF-α	1.40 (0.32-6.07)	4.50 (0.52-38.95)[3]
Inflammation composite	1.71 (0.81-3.62)	4.10 (1.08-15.56)

[1] Model 2 is adjusted for medication-resistant, age and gender after backwards stepwise regression

[2] Model 3 additionally adjusted for body mass index (CRP: n=44, IL-6, IL-10, and TNF-α: n=51)

[3] Unstable regression estimate

CRP = C-reactive protein, IL-6 = interleukin-6, IL-10 = interleukin-10, TNF-α = tumour necrosis factor-α, Inflammation composite = IL-6 and TNF-α, OR = odds ratio, CI = confidence interval

Supplemental Table 2. Correlation matrix between baseline levels of inflammatory markers and use of psychotropic medication during ECT

	Spearman's test for correlations			
	CRP	IL-6	IL-10	TNF-α
Psychotropic medication use during ECT	0.01	-0.11	-0.05	-0.05

CRP = C-reactive protein, IL-6 = interleukin-6, IL-10 = interleukin-10, TNF-α = tumour necrosis factor- α

CHAPTER 4

THE PATTERN OF INFLAMMATORY MARKERS DURING ELECTROCONVULSIVE THERAPY IN OLDER DEPRESSED PATIENTS

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ABSTRACT

Objectives

An association is found between changes in cytokine levels and antidepressant treatment outcome. Also, a proinflammatory profile is associated with a favourable electro-convulsive therapy (ECT) outcome. This paper investigates the pattern of inflammatory markers during a course of ECT in older depressed patients and whether this pattern is associated with ECT outcome. We hypothesized that ECT has an anti-inflammatory effect.

Methods

The pattern of CRP, IL-6, IL-10, and TNF-α during a course of ECT was examined using longitudinal mixed model analyses. Serum samples were collected in 99 older depressed patients (mean age: 72.8 ± 8.3 years, MADRS score 33.8 ± 9.0).

Results

After Bonferroni correction, there were no statistically significant alterations in levels of inflammatory markers during and after ECT. Effect sizes (Cohen's d) were -0.29 for CRP, -0.13 for IL-6, -0.06 for IL-10 and -0.07 for TNF-α. Changes in CRP or cytokine levels did not differ between remitters and non-remitters. Median baseline levels of CRP were significantly higher in remitters.

Conclusions

A small to medium effect size towards decreased CRP and IL-6 levels was observed. An anti-inflammatory effect of ECT could not be confirmed. However, the findings may suggest that patients with an inflammatory profile benefit more from ECT than other patients. Further studies are needed to confirm these findings.

INTRODUCTION

The relation between depression and inflammation has become clearer over the past years as findings of higher levels of cytokines and C-reactive protein (CRP) in depressed patients are extensively described.[1–4] For example; more than half (50 to 57%) of all depressed patients (both population-based and in- and outpatient samples) have moderately elevated levels of CRP (>1 mg/L), and about a quarter (16% to 27%) of patients experience low-grade inflammation (CRP >3 mg/L).[5] The overall pattern of inflammatory markers before and after pharmacological treatment for depression has been examined: three meta-analyses suggested a decrease in interleukin-6 (IL-6) of which two also found a decrease in interleukin-10 (IL-10) and tumour necrosis factor-alpha (TNF-α) after antidepressant medication.[6–8] Comparing these findings between responders and non-responders showed a decrease in TNF-α in responders only suggesting an association between nonresponse and persistent levels of TNF-α after antidepressant medication. A follow up of this meta-analysis[9] again found a decrease in TNF-α in responders and no differences in CRP, IL-6 and IL-10 between responders and non-responders.[6,9]

Along with antidepressant medication, electroconvulsive therapy (ECT) is a very effective treatment for depression.[10,11] It is hypothesized that a single ECT session increases inflammatory markers. Two reviews suggest that this initial immunological response is followed by a reduction in inflammatory markers at the end of the course of treatment suggesting an anti-inflammatory effect of ECT.[12–14] However, as depression is often accompanied by inflammation[1–4] it is also possible that the decrease in depressive symptoms causes the decrease in inflammatory markers and not necessarily a direct result of ECT. Other studies found no change in inflammatory markersafter ECT; an overview of studies examining inflammatory markers before and after ECT is given in Table 1.[15–24] Remarkably, one study[19] observed unchanged levels of IL-6 towards the end of ECT in the total group, however, a decrease in responders, suggesting that a decrease in inflammation is accompanied by a decrease in depressive symptoms. In addition, in a previous study, we found that patients with elevated levels of CRP have a favourable treatment outcome.[25] In light of the previous findings, this paper aims to investigate the pattern of inflammatory markers (CRP, IL-6, IL-10, TNF-α) during a course of ECT in older depressed patients and to investigate whether this pattern is associated with ECT outcome. If responders and non-responders show distinctive patterns of inflammatory markers during ECT, this may 1) provide insight into the

Table 1. Overview of studies examining changes in serum CRP, IL-6, IL-10 and TNF-α levels in depressed patients before and after ECT.

	n [1]	Mean Age	During ECT				After ECT			
			CRP	IL-6	IL-10	TNF-α	CRP	IL-6	IL-10	TNF-α
Hestad et al. 2003 [15]	15	55				=				_
Rotter et al. 2013 [16]	15	56		_	=	=		=	=	=
Zincir et al. 2016 [17]	50	33	n.d.					=	_	=
Rush et al. 2016 [18]	33	51	=	_	=	=	=	=	=	=
Järventausta et al. 2017 [19]	30	57		_				_ [2]		
Freire et al. 2017 [20]	31	45	n.d.					_		_
Kranaster et al. 2018 [21]	12	59	n.d.					=		
Kruse et al. 2018 [23]	29	43	_	_		=	=	=		=
Mindt et al. 2019 [24]	12	59	n.d.					=	=	=
Belge et al. 2020 [22]	62	58	n.d.					_		=
Carlier et al. (current article)	99	73	_	=	=	=	_	=	=	=

Only markers corresponding to ours are presented.

[1] Number of patients receiving ECT

[2] In remitters only

n.d. not determined

working mechanism of ECT and 2) help identify which patients can benefit from ECT. We hypothesize that ECT has an anti-inflammatory effect as is found in studies examining antidepressant medication.

METHODS

Participants

Data were collected from the Mood Disorders in Elderly treated with Electroconvulsive Therapy (MODECT) study.[26] In this prospective cohort study, 110 older patients were recruited from the inpatient population of two psychiatric hospitals: GGZ inGeest, Amsterdam, the Netherlands and the University Psychiatric Center KU Leuven, Belgium. The ethical committees approved all procedures involving patients of both hospitals. Written informed consent was obtained from all patients. Inclusion criteria consisted of older age (> 55 years), referral for ECT and the presence of a DSM-IV[27] unipolar depressive disorder. Exclusion criteria included bipolar disorder, a comorbid psychiatric disorder (for example schizoaffective disorder) or a neurological illness such as dementia, Parkinson's disease and stroke. Persons with missing serum samples were excluded from analysis (n=11). Age, sex, and depression severity were not associated with attrition.

Inflammatory markers

Serum samples of CRP, IL-6, IL-10, and TNF-α were available on three time points: one week before the start of ECT (T0), the third week during ECT (T1), and one week after finishing a course of ECT (T2). Median duration of a course was 11.0 (IQR = 7.0) sessions. Samples were collected between 07h30 and 09h30 and stored at -85 °C. Analyses of the inflammatory markers were performed as described before.[25] In short, immunoassays were performed at the Department of Clinical Chemistry of the University Medical Center, VUmc, in Amsterdam, the Netherlands. The high sensitive CRP kit (CRPHA) of Cobas was used to determine levels of CRP at the Endocrinology laboratory. Cytokine levels were determined using the Simoa Human Cytokine 3-Plex A assay kit at the Neurochemistry laboratory. All samples of one patient were assayed in one run and quality control samples were included. The intra- and inter-assay reproducibility coefficients amount 4.3% and 5.9% for IL-6, 3,9% and 5.3% for IL-10 and 4,2% and 5.3% for TNF-α, respectively.

Measures

Depression severity was measured before, weekly during and after a course of ECT using the Montgomery-Åsberg Depression Rating Scale (MADRS).[28] The scale has a range between zero and 60 points. Remission was defined as a MADRS score below 10 at two consecutive ratings.[29] Response was defined as a decrease in MADRS score of at least 50%.[30] Clinical and socio-demographic characteristics of patients were collected in a semi-structured interview as well as information on comorbid diseases such as cardiovascular diseases, rheumatoid disorders and diabetes mellitus.

ECT procedure

ECT was administered twice a week with the Thymatron System IV (maximum energy of 200%). According to Dutch guidelines[31], a dose titration protocol was used to determine stimulus intensity: initial seizure threshold x6 for right unilateral ECT and x2.5 for bilateral ECT. When the motor seizure duration was shorter than 20 seconds or the EEG seizure duration was less than 25 seconds, the dose was raised. [31] Patients started with unilateral ECT and were switched to bilateral ECT if clinical conditions worsened or if there was no clinical response after six ECT sessions. Two-third of patients received solely unilateral ECT. ECT was continued until patients achieved remission, or until no further clinical improvement was seen after a minimum of six unilateral and six bilateral sessions. Psychotropic medication was tapered off at least one week before ECT or was kept stable when discontinuing medication was considered impossible. In total, 8 and 14 patients continued to use antipsychotics and/or antidepressants, respectively.

Statistical analyses

Baseline characteristics are summarized in means with standard deviation (SD), median with interquartile range (IQR) and as percentages. Normality was examined using visual exploration of the data. To avoid bias as a result of inflammatory diseases and acute infection we excluded outliers according to Q1 – 3*IQR and Q3 + 3*IQR. Whenever an outlier was detected for CRP the entire sample on that time point was excluded. Four patients had outliers on two time points, 12 patients had outliers on one time point. A linear mixed model was performed to detect how inflammatory markers varied during ECT and how the pattern of inflammatory markers varied between subgroups of patients. Mixed model analysis was chosen as it allows for correlation between repeated measurements, it allows for multivariable analysis, and it allows for missing variables in the dependent variables, that is, inflammatory markers on three time points. The subgroups of patients were defined as remission

Table 2. Baseline characteristics of the sample of depressed patients treated with electroconvulsive therapy.

	Total	**Remission**	**No remission**	**T/X/U(df)**
	n = 99 [1]	n = 66	n = 32	*p*
Sociodemographics				
Age, years, mean (SD)	72.8 (8.3)	73.3 (8.2)	72.2 (8.5)	-0.6(96), 0.5
Women, No. (%)	66 (66.7)	42 (63.6)	23 (71.9)	0.7(1), 0.4
Inclusion site, Amsterdam, No. (%)	56 (56.6)	33 (50.0)	22 (68.8)	3.1(1), 0.1
Depression characteristics				
Baseline MADRS, mean (SD)	33.8 (9.0)	33.4 (8.5)	34.3 (10.1)	0.5(95), 0.7
MADRS after ECT, mean (SD)	9.6. (9.3)	4.3 (2.7)	20.4 (8.5)	13.9(95), <0.01*
Somatic morbidity				
Cardiovascular disease, No. (%)	47 (50.5)	31 (48,4)	17 (53.1)	0.2(1), 0.7
Inflammatory disease [2], No. (%)	35 (36.1)	23 (34.8)	12 (37.5)	0.1(1), 0,8
BMI, mean (SD), n=67	23.5 (4.1)	23.4 (3.9)	23.4 (4.0)	-0.0(64), 0.97
ECT characteristics				
ECT sessions, median (IQR)	11.0 (7.0)	10.0 (4.0)	14.0 (5.8)	628, <0.01*
Switched to bilateral ECT, No. (%)	31 (31.3)	9 (13.6)	22 (68.8)	30.2(1), <0.01*
Use of antidepressants, No. (%), n=82	14 (14.1)	8 (12.1)	5 (15.6)	0.2(1), 0.6
Use of antipsychotics, No. (%), n=82	8 (8.1)	6 (9.1)	2 (6.3)	0.2(1), 0.6

[1] Only 98 patients had values on remission.

[2] including rheumatoid disorder, diabetes mellitus, and chronic inflammatory lung diseases

SD = standard deviation, IQR = inter quartile range, No. = number, MADRS = Montgomery Åsberg depression rating scale

and non-remission and as responders and non-responders. All analyses were adjusted for age and sex. Additional adjustment for baseline depression severity was performed in the between-group analysis as depression severity can affect response and remission rates. A Bonferroni correction for multiple comparisons was used setting the statistical significance level at alpha=0.0125. Line graphs are plotted from univariable analyses for simplicity reasons. Post hoc analysis was performed to compare baseline median levels in inflammatory markers between remitters and non-remitters. Effect sizes (Cohen's d) were calculated for within-group changes in biomarkers and were interpreted according to Cohen's references: 0.2 small effect, 0.5 medium effect, and 0.8 large effect.[32] Analyses were performed using SPSS version 23 and STATA version 14.

RESULTS

Remission and response were reached in 66.7% (66/99) and 77.8% (77/99) of patients respectively (Table 2). In total, 90 serum samples were available before the start of ECT (T0), 83 at the third week of ECT (T1), and 86 one week after finishing an ECT course (T2). Attrition was differential concerning the number of chronic diseases in T0, that is, a higher number of chronic diseases was found in the excluded samples. Attrition was not associated with age, sex and depression severity.

Changes in inflammatory markers

CRP levels decreased after a course of ECT (β = -0.91; 95%CI=(-1.75,-0.08); Cohen's d = -0.29, p-value = 0.03, Figure 1) compared with baseline levels. Initially, CRP levels increased during ECT (β = 1.06; 95%CI=(0.22,1.91), p-value=0.01) compared with baseline levels with a medium effect size (Cohen's d = 0.34), see Figure 1. Both comparisons were not considered significantly different after Bonferroni correction. There were no statistically significant alterations in levels of IL-6, IL-10, and TNF-α during and after ECT compared to cytokines levels before ECT (Figure 1), and effect sizes were small (ranging from -0.11 to -0.13 for IL-6 and -0.04 to -0.07 for IL-10 and TNF-α). Results remained similar after adjustment for age and sex. Post hoc adjustment for baseline depression severity gave similar results.

Changes after ECT in remitters and non-remitters

Overall, no statistically significant changes in CRP and cytokine levels were found after a course of ECT both in remitters and non-remitters (Figure 1) and in responders and non-responders (data not shown); in non-remitters (n=33), small to medium effect

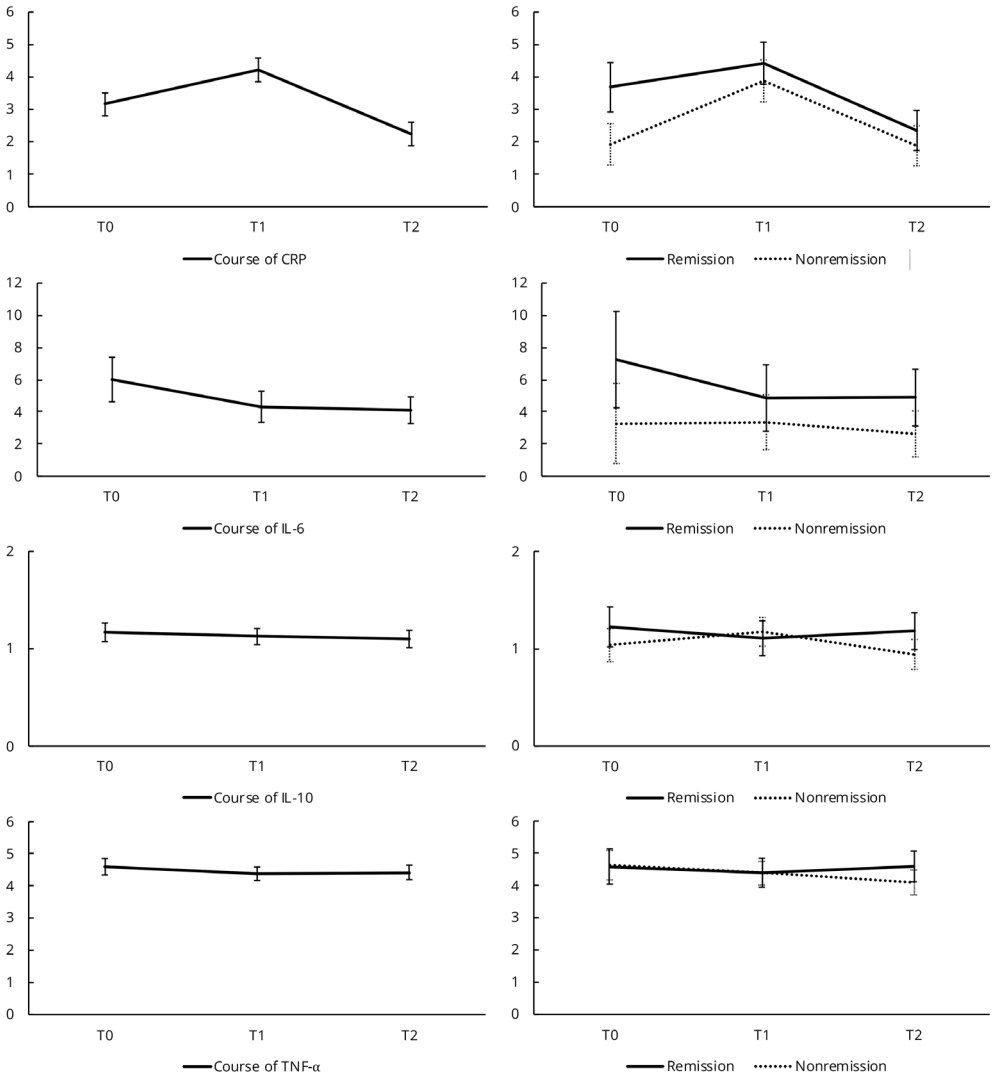

Figure 1. Predicted mean values of CRP, IL-6, IL-10 and TNF-α over the course of ECT in depressed older patients. T0 = before ECT, T1 = three weeks after start of ECT. T2 = one week after finishing ECT

Error bars represent standard error of the mean estimated with linear mixed model analysis. After correction for multiple comparisons, no significant differences were found over the course of ECT overall or between remitters and non-remitters. Effect sizes for changes in inflammatory markers after ECT were: Cohen's d: CRP = -0.29, IL-6 = -0.13, IL-10 = -0.06 and TNF-α = -0.07.

sizes were found for the decrease of CRP, IL-6, IL-10 and TNF-α after a course of ECT (Cohen's d = -0.02, -0.27, -0.31 and -0.54 respectively), and in remitters (n=66), the effect sizes of change after a course of ECT were: Cohen's d: CRP = 0.39, IL-6 = -0.13, IL-10 = -0.04 and TNF-α = 0.01. Results remained similar after adjustment for age, sex, and baseline depression severity.

Changes during ECT in remitters and non-remitters

The increase in CRP during ECT was different for remitters and non-remitters but was not considered statistically significant after Bonferroni correction for multiple comparisons. Overall, no statistically significant differences were found in levels of IL-6, IL-10 and TNF-α between remitters and non-remitters (Figure 1) and between responders and non-responders (data not shown). Results remained similar after adjustment for age, sex, and baseline depression severity.

In a post hoc analysis, CRP levels at baseline were compared between remitters and non-remitters showing higher levels in remitters (Remitters: median 2.8 mg/L, Non-remitters: 1.0 mg/L, Mann-Whitney U=534, p <0.01). The baseline levels of IL-6, IL-10 and TNF-α did not differ between groups.

DISCUSSION

This study aimed to investigate the pattern of inflammatory markers during a course of ECT in older depressed patients to gain insight in the working mechanism of ECT and to provide information on which patients could benefit from ECT. The results show no statistically significant alterations in serum cytokine and CRP levels after ECT, after a Bonferroni correction was made, although both for CRP and IL-6 a small to medium effect size towards a decrease at the end of treatment was seen. This pattern of inflammatory markers is similar in remitters and non-remitters and responders and non-responders. Patients who remitted had higher levels of baseline CRP. These findings strengthen the possibility that especially patients with an inflammatory profile benefit from treatment such as ECT.

Findings from comparable studies on changes in inflammatory markers after ECT are summarized in Table 1. Although the sample sizes are small, overall, most studies are consistent with our findings, that is, unchanged levels of IL-10 and TNF-α after a course of ECT. Remarkably, in antidepressant medication studies, levels of TNF-α in particular decrease after treatment[8,9], suggesting a distinct working mechanism for

antidepressant medication as compared to ECT. In our study, a small to medium effect size was found for a decrease in levels of CRP and IL-6 after ECT compared to pre-ECT levels (the decrease in CRP lost its statistical significance after Bonferroni correction). Contrary to our findings, two studies found no change in CRP levels after ECT.[18,23] For IL-6, a decrease towards the end of ECT was found in three studies compared to five studies that found no change (Table 1). We would expect to find similarities in the pattern of CRP and IL-6 as they are interdependent: CRP can induce IL-6 production while IL-6 can induce secretion of CRP.[33] With the current findings, it remains unclear whether ECT has an anti-inflammatory effect even though some studies point in that direction.

Apart from examining the anti-inflammatory effect of ECT, we performed subgroup analyses to examine whether patients with a favourable treatment outcome have different CRP or cytokine patterns during ECT. No statistically significant differences were found in the overall pattern of CRP, IL-6, IL-10 and TNF-α between remitters, non-remitters, responders, and non-responders. To our knowledge, our study is the third study examining the pattern of inflammatory markers stratified for treatment outcome. The two previous studies found a decrease in IL-6 towards the final ECT session in remitters only[19], and a trend towards decreased IL-6 levels in responders only.[22] In our study, a medium effect size for the decrease in IL-6 in non-remitters was found, however, we believe it was distended by the small number of non-remitters (22/99). Besides, a small effect size was found for the decrease in IL-6 in remitters and the total sample. Our study differs from most previous studies as we used a linear mixed model rather than a paired difference test (Wilcoxon, Kruskal-Wallis or paired T-test), allowing for confounder adjustment and missing values, leading to more reliable results. The present findings indicate that even if ECT would have anti-inflammatory properties, it is independent from therapeutic effect. In a previous study, we found that patients with higher levels of CRP before ECT are more likely to remit from depression after ECT.[23,25] We were interested whether alterations in CRP levels during ECT corresponded between remitters and non-remitters. The present findings suggest that the CRP and cytokine patterns were independent from ECT outcome. Although not the primary focus of our study, we found that levels of CRP were higher at baseline in remitters compared to non-remitters. Similar findings are described for IL-6 levels and a trend for CRP levels in a comparable study.[23] This may suggest that patients with higher levels of inflammation are most likely to benefit from ECT. In comparison, recent meta-analyses have found that antidepressant medication response is

independent from baseline levels of inflammation.[9] If these findings are confirmed, personalized treatment plans could include some patients being treated with medication and others - patients with an inflammatory profile or higher baseline CRP - with ECT.

The concept that anti-inflammatory properties are important in the treatment of depression is not new.[34,35] Several meta-analyses examined whether changes in cytokine levels were associated with antidepressant treatment outcome.[7–9,36] The high amount of nonresponse with traditional antidepressants have stimulated the search for other treatment options for depression. Studies have shown that monotherapy or add-on therapy with anti-inflammatory agents such as non-steroidal anti-inflammatory drugs (NSAID), cytokine inhibitors, or statins, can reduce depressive symptoms.[37–40] This effect is also seen in patients with chronic inflammatory diseases where depressive symptoms were measured as a secondary outcome measure.[41] Antidepressant treatments with anti-inflammatory properties may be especially effective in patients who experience higher baseline inflammation, for example, patients with inflammatory diseases. This hypothesis is strengthened by the above-mentioned finding that higher baseline levels of CRP are associated with higher chances of remission after ECT.[23,25]

Strengths and limitations

A strength of this study is the relatively large sample size compared to similar studies. As a result of this, we were able to compare patterns of inflammatory markers in subgroups of patients. Another strength is the use of linear mixed model analysis for longitudinal data, allowing us to control for confounding variables. The use of an older patient group hampers comparison of our findings with other studies. However, inflammation is more common in older patients[42–44], therefore it is important to look at the relationship between inflammation and ECT in older people. Unknown is whether the differences in inflammation levels between older patients may be smaller than in adults possibly causing an underestimation of changes in cytokine pattern during ECT. Next, some patients used antipsychotic and antidepressant medication, both have been found to alter inflammatory markers.[45] A consideration was whether to correct for multiple testing. This study included analyses of four biomarkers in remitters, non-remitters, responders and non-responders, thus, we corrected for multiple testing to reduce the risk of a type I-error. However, this decision automatically increases the risk of rejecting a true H1 hypothesis.[46] The use of effect sizes assists in interpreting our findings. A control group would facilitate comparison of the pattern of inflammatory markers within depressed patients not

receiving ECT. Finally, the use of stimulated cytokines, that is, measurement of cytokines in blood samples after adding lipopolysaccharide, would facilitate in measuring the cytokine production capacity and could be considered in future studies.

In conclusion, in this relatively large sample of older depressed patients receiving ECT, a small to medium effect size towards decreased CRP and IL-6 levels after a course of ECT was found. Patients who remit after ECT have similar patterns of inflammatory markers during ECT as patients who do not remit, albeit remitters had higher levels of baseline CRP. With the present findings, an anti-inflammatory effect of ECT could not be confirmed. However, the findings suggest that patients with an inflammatory profile benefit more from ECT than other patients. Further research, for example, including patients with higher inflammatory markers, is needed to confirm these findings.

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CHAPTER 5

THE COURSE OF APATHY IN LATE-LIFE DEPRESSION TREATED WITH ELECTROCONVULSIVE THERAPY

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ABSTRACT

Objectives

Apathy, a lack of motivation, is frequently seen in older individuals, with and without depression, with substantial impact on quality of life. This prospective cohort study of patients with severe late-life depression treated with electroconvulsive therapy (ECT) aims to study the course of apathy and the predictive value of vascular burden and in particular white matter hyperintensities on apathy course.

Methods

Information on apathy (defined by a score of >13 on the Apathy Scale), depression severity, vascular burden, and other putative confounders was collected in at two psychiatric hospitals on patients with late-life depression (aged 55 to 87 years, N=73). MRI data on white matter hyperintensities were available in 52 patients. Possible risk factors for apathy post-ECT were determined using regression analyses.

Results

After treatment with ECT, 52.0% (26/50) of the depression remitters still suffered from clinically relevant apathy symptoms. In the entire cohort, more patients remained apathetic (58.9%) than depressed (31.5%). Presence of apathy post-ECT was not associated with higher age, use of benzodiazepines, or severity of apathy and depression at baseline. Less response in depressive symptomatology after ECT predicted post-treatment apathy. The presence of vascular disease, diabetes mellitus and smoking, and white matter hyperintensities in the brain was not associated with post-treatment apathy.

Conclusions

Apathy may perpetuate in individual patients, despite remission of depressive symptoms. In this cohort of patients with late-life depression, post-ECT apathy is not associated with white matter hyperintensities.

INTRODUCTION

Apathy is defined as "a lack of motivation that is not attributable to a diminished level of consciousness, cognitive impairment or emotional distress".[1] Apathy is frequently present in older individuals (>65) and patients with neurological and psychiatric disorders such as Alzheimer's disease, Parkinson's disease, frontotemporal dementia, stroke and major depression.[1–4] The impact of apathy on quality of life is substantial.[5,6] To date, it remains unclear whether apathy is an independent behavioral syndrome; albeit studies increasingly recognize it as such.[2,5,7–12] In the context of depressive illness apathy is a complex issue. Since symptoms partly overlap, it remains an endeavor to disentangle to what extent lack of motivation is a depressive symptom or part of an independent syndrome. Insight in this complex matter may be derived from studies on the course of apathy in depression treatment.

To our knowledge, two randomized clinical trials[13,14] and one prospective cohort study[5] have investigated the course of apathy in older patients with depression. The first two studies investigated the course of apathy during treatment with selective serotonin reuptake inhibitors (SSRI), both demonstrating an improvement in depression severity and a partial response of apathy symptoms, independent from each other.[14] The longitudinal, naturalistic study of Groeneweg-Koolhoven et al.[5] demonstrated 80% persistence of apathy and 41% persistence of depression in a group of 199 older persons with depression during 2-year follow-up.

It has been suggested that apathy is strongly linked with white matter hyperintensities (WMH)[9,15–21] and, therefore, post-depression-treatment apathy may be (partly) due to vascular brain damage. To date, studies that have examined the impact of WMH on post-depression-treatment apathy are scant. Yuen et al.[14] investigated the impact of neuroanatomical correlates on the response of apathy to SSRI treatment in depressed non-demented, older persons. They found that structural brain changes may interfere with prefrontal cortical recruitment of limbic activity, which is essential for motivated behavior. This could, at least partly, explain the persistence of apathy during and after depression treatment.

Electroconvulsive therapy (ECT) is the most effective treatment for severe depression.[22,23] In addition, ECT enhances the dopamine-pathways more than antidepressants.[24] Dopamine is reckoned to be at the core of motivated behavior. Research into the course of apathy in depressed persons during ECT and the role of vascular burden and in

particular WMH reflecting ischemic small vessel disease may provide further insight into this complex matter. The Mood Disorders and ECT study (MODECT), a prospective cohort study consisting of older persons referred for ECT, provides an excellent opportunity to study the course of apathy during ECT since information on depression severity, apathy, vascular disease, and WMH is available.[25] Based on prior studies[5] we hypothesize that a majority of older depressed persons will have significant symptoms of apathy, despite remission of depressive symptoms following ECT treatment. In addition we hypothesize that post-depression-treatment apathy is associated with WMH.

METHODS

Study sample

Data in this study were derived from the MODECT, a prospective cohort study.[25,26] In total, 110 older persons (age >55 years) with a unipolar major depressive disorder according to the DSM-IV criteria[27] referred for ECT, were recruited from two psychiatric hospitals (GGZinGeest, Amsterdam, the Netherlands and University Psychiatric Center, KU Leuven, Belgium). Exclusion criteria were a major neurological illness (including dementia and Parkinsons's disease), or a DSM-IV diagnosis of bipolar- and schizoaffective disorder. Diagnoses were made by a psychiatrist and confirmed by the Mini-International Neuropsychiatric Interview.[28] Persons with missing values on the Apathy Scale (AS) at baseline (before the start of ECT) and one week after final ECT session were excluded (n=37). Attrition was differential with respect to baseline psychomotor symptoms, which was higher for excluded subjects. Other factors (age, sex, years of education, life threatening symptoms as primary indication for ECT, depression severity, age of onset, cognitive functioning, vascular burden and in particular WMH) were not associated with attrition.

ECT procedures

Patients received ECT twice weekly, preferably starting with right unilateral stimuli. All treatments were administered using the Thymatron System IV (maximum energy 200%, 1008 mCoulombs) using a titration dosing protocol. A motor seizure duration less than 20 seconds or a seizure duration less than 25 seconds on EEG recordings was considered inadequate, after which the dose was raised according to Dutch guidelines.[29] If clinical condition worsened, i.e. increase in total MADRS scores, increased suicidality, dehydration or weight loss, occurrence of psychotic features or if no clinical improvement occurred after six ECTs, a switch to bilateral ECT was applied. ECT was continued until remission - defined as Montgomery Asberg Depression Rating Scale (MADRS) scores lower than

ten at two successive ratings – was achieved, or when no further improvement occurred during two weeks, despite sufficient treatments (e.g. a minimum of six unilateral and six bilateral sessions). Psychotropic medications, e.g. antidepressants, anti-epileptics, and benzodiazepines, were tapered off within two weeks before start of ECT treatment.

Measures

Clinical assessments were conducted before start of treatment (T0) and one week after completion of treatment (T1). Apathy was assessed with the Apathy Scale (AS), which has 66% sensitivity and 100% specificity to categorize patients as apathy versus no apathy (validated in Parkinson disease patients).[30,31] The AS consists of 14 items, each with a four-answer scale (0-3; not at all, slightly, some, and a lot). Post-depression-treatment apathy (further on mentioned as post-treatment apathy), was defined as a score on the AS higher than 13, higher scores indicate more severe apathy.[30,32] Information on discriminant validity is not available. However since the AS is based on the Apathy Evaluation Scale, a comparable good discriminant validity is assumed.[31,33] The MADRS was used to measure severity of depression. It consists of ten questions rated from 0-6 with a total score 60.[34] Early age of onset was defined as an onset of depression before 55 years. Somatic history was assessed prior to treatment in a semi-structured interview and included pulmonary disorders, arthrosis, (rheumatoid) arthritis, malignant neoplasms, migraine, thyroid disease, Parkinson's disease, other disease of the central nervous system, consequences of an accident (fractures, head injury or burns) and permanent disability due to surgery. Vascular disease was defined as a history or current treatment of hypertension, myocardial infarction (MI) and cerebrovascular disease. Additionally a variable vascular burden was defined as presence of at least one of the following conditions: vascular disease, diabetes mellitus (DM) or smoking. Smoking was categorized as never or ever (including current use) and alcohol use as less than monthly or two times a month or more. Cognitive functioning was assessed by the Mini-Mental State Examination (MMSE, range 0-30)[35] and was conducted weekly. Psychomotor symptoms including, agitation, retardation and non-interactiveness were measured using the 18-item CORE assessment of psychomotor symptoms, total score range from 0 to 54.[36] Finally, for apathy (AS), depression severity (MADRS) and psychomotor symptoms, change scores were calculated by subtracting the total score at T1 from T0.

Magnetic resonance imaging (MRI)

MRI data were analyzed on the presence and severity of WMH by an independent neuroradiologist. A validated visual rating scale established by Fazekas[37] was applied in

order to grade the severity of deep subcortical white matter hyperintensities (subcortical WMH): 0 (no or single punctate white matter lesions), 1 (punctate white matter lesions), 2 (beginning confluent lesions), 3 (large confluent lesions). In addition, periventricular white matter hyperintensities (periventricular WMH) were assessed on a three-point scale: 0 (no structural abnormalities), 1 (thin lining lesions), 2 (>5mm lesions).[37] All MRI measures were rated on FLAIR images. In our sample of 73 patients, MRI data were available for 52 people (71%) which were all included in analysis. Attrition analysis showed that persons with missing MRI data were comparable for all dimensions to those with MRI data.

Statistical analyses

Comparisons of the distribution of characteristics across post-treatment apathy and no post-treatment apathy were made using the two-tailed chi-square test for dichotomous variables, and the Student T-test or Mann-Whitney U-test for continuous variables. Assumptions of normality were made with use of skewness and kurtosis measurements. In addition, in a subsample of persons with remission of depression, the number of persons with post-treatment apathy was calculated. Pearson's or Spearman's test for correlations were used to examine correlations between change scores in MADRS, AS, vascular disease, alcohol use and WMH. To determine which clinical characteristics might predict post-treatment apathy after ECT treatment we performed multivariate logistic regression analyses. Odds ratio's (OR) are presented with their 95% confidence intervals (CI). Demographic variables (age, sex), vascular burden (hypertension, myocardial infarction, diabetes mellitus, cerebrovascular disease, smoking) and MRI measures (subcortical WMH and periventricular WMH) were entered in the model. MRI measures were entered in the models separately. Additionally, multicollinearity was tested. The same analysis was performed using linear regression. Effect sizes were calculated for all vascular burden measures using Cohen's d and were interpreted according to Cohen's widely used references; 0.2 small effect, 0.5 medium effect, 0.8 large effect.[38] All analyses were conducted using SPSS version 20.

RESULTS

Patient characteristics

Apathy was present at baseline in 93.2% (68/73) of patients (AS>13) with a total mean AS score of 24.7 (SD ± 7.4). The mean population age was 71.9 years (range 55-87 years) and 47 patients (64.4%) were women (Table 1). 50 patients out of 73 (68.5%) remitted from depression after ECT treatment (MADRS <10).

Table 1. Baseline characteristics, vascular burden and white matter hyperintensities in the total cohort split up for post-treatment apathy and no apathy.

	Total n = 73	**No Apathy** [1] n = 30	**Apathy** [1] n = 43	**T/X/U(df)** *p*
Sociodemographic				
Age, years, mean (SD)	71.9 (8.8)	69.5 (8.4)	73.5 (8.9)	-1.9(71), 0.05
Women, No. (%)	64.4	63.3	65.1	0.02(1), 0.9
Level of education in years, median (IQR)	9 (3)	9.5 (6)	9 (1.3)	377, 0.3
Age of onset, early <55y, No. (%)	46.6	43.3	48.8	0.2(1), 0.6
Baseline MMSE, median (IQR)	26 (5.3)	26 (6)	26 (5)	427, 0.8
Highest MMSE, median (IQR)	29 (3)	28.5 (3.3)	29 (4)	631, 0.9
MMSE after ECT, median (IQR)	27 (4)	27 (4)	28 (4.5)	533, 0.8
Baseline MADRS, mean (SD)	32.7 (8.6)	33.3 (7.8)	32.2 (9.2)	0.5(66), 0.6
Δ MADRS; mean (SD)	23.2 (11.4)	28.4 (8.3)	19.7 (12)	3.3(66), <0.01
Baseline AS, mean (SD)	24.7 (7.4)	23.5 (8.4)	25.6 (6.6)	-1.1(52), 0.3
Δ AS, mean (SD)	8.3 (8.7)	13.7 (8.3)	4.4 (6.7)	5.3(71), <0.01
Baseline CORE, mean (SD)	13.7 (7.9)	14.7 (8.4)	13.1 (7.7)	0.8(64), 0.4
Δ CORE, mean (SD)	9.5 (8.6)	12.7 (8.7)	7.4 (8.1)	2.5(63), 0.02
Benzodiazepines use, No. (%)	46.6	50	44.2	0.2(1), 0.6
Alcohol use, No. (%)	20.6	25.9	17.1	0.8(1), 0.4

[1] Apathy defined as AS 14-42, No apathy defined as AS<14

SD = Standard Deviation, IQR = Inter quartile range, MMSE = Mini-mental State Examination, Highest MMSE = Highest score in the course of treatment, CORE = CORE assessment of psychomotor symptoms, MADRS = Montgomery Asberg Depression Rating Scale, AS = Apathy Scale

Table 1. Continued

Vascular burden, No. (%)				
Hypertension	31.9	31	32.6	0.02(1), 0.9
Myocardial infarction	29.2	24.1	32.6	0.58(1), 0.3
Smoking	38.1	44	34.2	0.6(1), 0.4
Diabetes Mellitus	6.9	3.4	9.3	0.9(1), 0.3
Cerebrovascular disease	1.4	0	2.3	0.68(1), 0.4
Subcortical WMH, mean (SD), n=52	1.2 (0.8)	1.1 (0.7)	1.3 (0.8)	-0.98(50), 0.3
Periventricular WMH, mean (SD), n=52	1.1 (0.7)	1 (0.6)	1.2 (0.7)	-1.2(50), 0.3

SD = Standard Deviation, WMH = White matter hyperintensities

Apathy after ECT treatment

Post-treatment apathy was seen in 43 patients (58.9%), with a mean AS score of 21.1 (SD ± 4.9). In these patients, the average decrease in AS was 10.6% (SD ± 16.0%) from baseline compared to 32.7% (SD ± 19.8%) in patients without post-treatment apathy. In the entire cohort more patients remained apathetic (58.9%) than depressed (31.5%). As shown in Table 2, 23 of 41 (56.1%) post-treatment apathy patients showed remission of depression. The mean baseline MADRS for all patients was 32.7 (SD ± 8.6), indicating severe depression in this hospitalized cohort. Mean decrease in MADRS was 23.2 (SD ± 11.4). There were no significant differences in clinical characteristics, vascular disease, and the presence of WMH across post-treatment apathy and no apathy groups. Pearson's test for correlation indicated a positive association between change scores in MADRS and the AS (0.57), change scores in MADRS and CORE (0.68) suggesting an overlap in measurements. Little improvement in depressive symptoms (total MADRS score) proved to be a significant predictor of post-treatment apathy after ECT treatment in univariate analyses, OR = 0.9; 95%CI = (0.87-0.98), whereas older age, OR = 1.06; 95% CI = (0.99-1.12), use of benzodiazepines, OR = 0.79; 95%CI = (0.31-2.02), age of onset, OR = 0.8; 95%CI = (0.31-2.05), high baseline apathy scores, OR = 1.04; 95%CI = (0.98-1.11) and high baseline MADRS scores, OR = 0.99; 95%CI = (0.93-1.04) were not. Since late-life depression is associated with neurodegenerative disorders, pre-clinical dementia should be considered as a possible cause of apathy in our sample.[39] Therefore post-hoc analyses were performed. First, the highest score of the weekly MMSE-measurements during the course of ECT were determined. MMSE scores <24

Table 2. Within group frequencies (n = 73)

	Remission of depression	No remission of depression
Post-treatment apathy, Apathy at baseline	23, 46.0%	18, 78.3%
Post-treatment apathy, No apathy at baseline	3, 6.0%	0
No post-treatment apathy, Apathy at baseline	22, 44.0%	5, 21.7%
No post-treatment Apathy, No apathy at baseline	2, 4.0 %	0
Total	50	23

were considered as poor cognitive functioning, susceptible for putative pre-clinical dementia. Next, associations between poor cognitive functioning and apathy groups were examined. No statistical differences were found in poor cognitive functioning between Apathy and No apathy groups, X2(1) = 0.01, p = 0.61. Likewise, in univariate analysis a MMSE score of <24 did not prove to be a significant predictor of post-treatment apathy, OR = 0.9; 95%CI = (0.19-4.46). Finally, baseline MMSE and post-treatment MMSE scores did not prove to be predictors of post-treatment apathy, respectively OR = 1.0; 95%CI = (0.89-1.13) and OR = 0.95; 95%CI = (0.82-1.11). Additionally, bilateral ECT is thought to have a higher impact on cognition than unilateral ECT and therefore the number of patients with post-treatment apathy, stratified for unilateral or bilateral ECT, was examined in a post-hoc analysis. In patients who received unilateral ECT (n = 50), 48% of the patients with apathy at baseline were also apathetic at follow-up. In patients who received solely bilateral ECT (n = 4) or who shifted toward bilateral ECT (n = 18), 77.3% of the patients with apathy at baseline remained apathetic. Regression analyses were additionally adjusted for ECT-technique. However, findings remained largely similar: Model 1 OR = 0.98; 95%CI = (0.54-1.77), Model 2 OR = 0.95; 95%CI = (0.49-1.86), Model 3 OR = 0.87; 95%CI = (0.43-1.77) and Model 4 OR 0.81; 95%CI = (0.33-1.95).

Apathy and vascular burden

In multivariate analyses, we examined the association between post-treatment apathy and vascular burden including hypertension, MI, DM, cerebrovascular disease, smoking, and WMH (subcortical WMH and periventricular WMH). As shown in Table 3, all vascular and MRI measures were entered in separate models, adjusted for age, sex, and change scores in MADRS. In both model 1 and model 2 older age (OR = 1.09; 95%CI = (1.02-1.17)

and change score in MADRS (OR = 0.91; 95%CI = (0.86-0.97) were significantly associated with post-treatment apathy. After adjustment for subcortical WMH and periventricular WMH in model 3, change score in MADRS, OR = 0.94; 95%CI = (0.88-0.99), remained a predictor for post-treatment apathy, whereas older age, OR = 1.08; 95%CI = (0.99-1.18) did not. Vascular burden, OR = 0.8; 95%CI = (0.2-3.11), and smoking, OR = 0.5; 95%CI = (0.14-1.76), was not associated with post-treatment apathy. Model 3 shows the Fazekas scale, e.g. subcortical WMH and periventricular WMH, and was added separately to multivariate analyses, showing the absence of an association with post-treatment apathy (Subcortical WMH: OR = 1.07; 95%CI = (0.39-2.95) and Periventricular WMH: OR = 1.04; 95%CI = (0.34-3.17). When entered in the model together with vascular burden (model 4) none of the measures was associated with post-treatment apathy (see Table 3).

Table 3. Multivariate logistic regression analyses on post-treatment apathy.

	Model 1	**Model 2**	**Model 3**	**Model 4**
	n = 68	n = 58	n = 50	n = 41
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Demographics				
Age	1.09 (1.02-1.17)	1.08 (1.00-1.16)	1.08 (0.99-1.18)	1.07 (0.97-1.18)
Sex	0.76 (0.23-2.58)	0.62 (0.15-2.55)	1.07 (0.29-3.98)	0.96 (0.19-4.98)
Psychopathology				
Delta MADRS	0.91 (0.86-0.97)	0.92 (0.86-0.98)	0.94 (0.88-0.99)	0.94 (0.88-1.00)
Vascular burden				
Smoking	-	0.50 (0.14-1.76)	-	0.6 (0.13-2.66)
Vascular disease	-	0.80 (0.2-3.11)	-	0.86 (0.18-4.05)
MRI Measures [1]				
Subcortical WMH	-	-	1.07 (0.39-2.95)	1.01 (0.34-3.02)
Periventricular WMH	-	-	1.04 (0.34-3.17)	0.81 (0.21-3.11)

[1] MRI measures are entered in the model separately. The odds ratios presented represent the model including subcortical WMH

WMH = White matter hyperintensities, OR = odds ratio, CI = confidence interval, MADRS = Montgomery Åsberg Depression Rating Scale

There was no multicollinearity among predictor variables as their variance inflation factors were <2.0. Outcomes of linear regression analyses, using apathy change scores, were similar to fore mentioned results. Effect sizes were calculated for all measures of interest. Cohen's effect size value for subcortical WMH (d = 0.27) and periventricular WMH (d = 0.31) suggested a small to moderate impact of WMH on post-treatment apathy.

DISCUSSION

The results of our study suggest that apathy, defined by a score of >13 on the Apathy Scale (AS), is seen in almost two third (58.9%) of all patients after treatment with ECT. In total, 31.5% of patients showed persistence of depressive symptoms (MADRS>10). The larger number of patients with apathy as compared to persistence of depression suggests that a considerable number of persons suffer from post-treatment apathy, despite remission of depressive symptoms. This was confirmed by the finding that half of the remitted depression patients (26/50, 52.0%) still reported clinically relevant apathy symptoms. A smaller decline in MADRS scores, however, was predictive of post-treatment apathy. Contrary to our hypothesis, there were no differences in vascular burden and in particular WMH between patients with or without post-treatment apathy.

Our findings are in line with Yuen et al.[14], who demonstrated a clinically significant decrease in apathy symptoms following treatment with escitalopram. In their sample of older persons with depression, 43.8% had post-treatment apathy according to the Apathy Evaluation Scale. Depression severity decreased to a larger extent than did apathetic symptoms.[14] The impact of post-treatment apathy on prognosis is substantial; Groeneweg-Koolhoven et al.[5] showed that older persons with persistent apathy at two year follow-up were less likely to recover from depression than those that remitted from apathy. As was demonstrated by our findings, a smaller decline in total MADRS score was associated with the presence of post-treatment apathy. In addition, changes in scores of MADRS and AS were correlated (Pearson: 0.57) contributing to the idea of overlapping symptoms in depression and apathy, and apathy as a residual symptom of depression. In contrast, our findings showed higher recovery rates for depression as compared to apathy. Furthermore, severity of apathy and depressive symptoms at baseline did not predict post-treatment apathy, which suggests different etiologies for apathy. Finally, the impact of ECT on cognitive functioning, which may clinically manifest as apathy, must be considered. This may particularly be seen in persons with bilateral ECT, considering the greater impact of bilateral ECT on cognitive functioning.[40] However, as post-hoc

analyses showed no influence of ECT technique on the presence of post-treatment apathy, an overestimation of apathy by means of interference with cognitive functioning is less plausible.

Next, we examined to what extent vascular burden may be associated with post-treatment apathy. We hypothesized that post-treatment apathy would be associated with vascular burden including a history of MI, hypertension, DM, vascular disease, smoking and WMH measured using the Fazekas scale. However, vascular burden was not significantly associated with the course of apathy during ECT. Similar to our results, Lampe and Heeren[41] did not find an association between apathy and vascular risk in a cross-sectional study on 29 depressed older persons. In contrast, other studies have repeatedly indicated motivational symptoms as a characteristic of white matter lesions, lacunar infarcts or vascular disease both in presence and absence of depression.[3,16–18,42–44] Probably, post-treatment apathy may be a final common pathway of various underlying pathophysiological mechanisms, especially in this cohort of persons with late-life depression. Further studies are needed to further elucidate this complex matter.

Some limitations should be noted. Depression is associated with neurodegenerative disorders, therefore the possibility of apathy not being related to depression in some patients yet being related to pre-clinical dementia must be considered. Oudega et al.[39] presented a naturalistic follow-up study (N=39) demonstrating 65.1% of patients with cognitive decline and 17.9% diagnosed with dementia 7-12 years after ECT treatment. In post-hoc analyses, we could not demonstrate an association between poor cognitive functioning and apathy, possibly suggesting that poor cognitive function does not contribute to apathy in our cohort. However, the MMSE used in our study has its limitations in characterizing cognitive deficits during ECT. The use of more detailed cognitive testing must be considered in future research. In conclusion, post-treatment apathy may in some patients be a clinical warning for future cognitive decline and dementia. Studies with longer follow-up are warranted to gain insight in the course of cognitive decline in persons with post-ECT apathy. In addition, previous studies demonstrated that WMH, are important foci in patients suffering from apathy.[14,16,45,46] These measures were therefore included in the MODECT-study. However, other studies suggest other regions of interest to be associated with apathy. For example, the volume of acute pontine infarcts is suggested to predict post-stroke apathy while periventricular WMH do not.[44] In general, subcortical frontal brain regions seem important in the association between apathy and depression.[7] Apart from the applied MRI measures,

our analysis included global cortical atrophy[47,48] and medial temporal lobe atrophy.[46] However, both did not show a significant association with apathy. Including different brain regions must be considered in further research. Another limitation is the use of the Apathy Scale, which is validated in older persons with Parkinson disease and dementia. Albeit frequently used in research into apathy in depressed persons, unfortunately, the discriminant validity in depression is not available. In further research use of the Apathy Evaluation Scale should be considered.[31,33] In addition, four-week follow-up measurements were not included in the analysis because of the large amount of missing AS data (62%). Therefore we do not know whether the improvement of apathy continued after the end of treatment. In future research, including qualitative comments from participants on the impact of depression and apathy pre- and post-treatment should be considered.

Conclusion

In conclusion, our results indicate that two thirds of patients with late-life depression show apathy after treatment with ECT, as do 52% of those who achieved remission of depression after ECT. As the impact of apathy on prognosis and quality of life is substantial[5,6], it is important to acknowledge this high prevalence and consider apathy as an invalidating independent behavioral syndrome. Moreover, the present results suggest that apathy may not be relieved by depression treatment and need a distinctive approach.

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Part II:
Biomarkers and cognition

CHAPTER 6

INFLAMMATION AND COGNITIVE FUNCTIONING IN DEPRESSED OLDER ADULTS TREATED WITH ELECTROCONVULSIVE THERAPY; A PROSPECTIVE COHORT STUDY

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ABSTRACT

Objectives

Despite its effectiveness, patients and practitioners are often reluctant to start electroconvulsive therapy (ECT) due to the risk of transient cognitive side effects, particularly in older patients. Inflammatory processes may be associated with the occurrence of these effects. We assessed whether inflammatory markers prior to ECT are associated with cognitive functioning in depressed patients treated with ECT.

Methods

Between 2011 and 2013, 97 older patients (mean age 73.1±8.1 years) with severe unipolar depression (according to the DSM-IV) referred for ECT were included. We used Mini-Mental State Examination (MMSE) scores to determine cognitive functioning prior to, weekly during, and in the first week after a course of ECT. Serum levels of C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-10 (IL-10), and tumour necrosis factor-α (TNF-α) were assessed prior to ECT.

Results

In fully adjusted models, there was an association between TNF-α and cognitive functioning: β = -1.05; 95%CI=(-2.04 to -0.06), f2 = 0.06). An association was also found between baseline levels of IL-10, TNF-α and lower MMSE scores during ECT: IL-10: β = -2.03; 95%CI=(-3.16 to -0.89), TNF-α: β = -0.66; 95%CI=(-1.08 to -0.24). In addition, an association was found between baseline CRP and lower MMSE scores directly after a course of ECT: β = -0.51;95%CI=(-0.93 to -0.09), f2 = 0.10). Associations with IL-6 did not reach significance.

Conclusions

This study suggests that inflammatory processes are associated with lower cognitive functioning prior to ECT, and predispose for (further) cognitive dysfunction during and after a course of ECT.

INTRODUCTION

Electroconvulsive therapy (ECT) is one of the most effective treatments for major depression, especially in older patients.[1] Despite its effectiveness, patients and practitioners are often reluctant to start ECT[2], partly due to fear of memory impairment.[3,4] Indeed, several cognitive side effects with a range of manifestations and impact have been described, varying from post-ictal delirium[5,6] to retrograde amnesia.[7,8] In general, studies demonstrated that cognitive side effects are transient.[8–13] Meta-analyses described declined cognitive performance in the first three days after finishing a course of ECT and improved cognitive performance, back to baseline or beyond baseline levels, in the following 12 days.[8] Similarly, studies on long-term cognitive functioning, measured with a cognitive test battery six months after ECT, showed no decline in cognitive performance as compared to cognitive functioning prior to ECT.[14,15]

Nonetheless, transient cognitive side effects increase treatment burden by leading to worse daily functioning, higher care demands, poorer quality of life and fear for ECT, which may result in a barrier and non-adherence to treatment.[3,4] Being able to give information on individual risk for cognitive side effects to patients and family members will help avoid premature discontinuation of ECT.[16–18] Moreover, strategies for minimizing cognitive side effects are being developed, that is, cognitive training[19], administration of thyroid hormone[20], erythropoietin[21,22], and acetylcholinesterase inhibitors.[23,24] To further develop strategies that minimize cognitive side effects and to identify patients at risk, insight into the underlying pathophysiology of cognitive functioning during a course of ECT is needed. Known patient characteristics associated with cognitive functioning during or directly after ECT include poor baseline cognitive functioning and smaller hippocampal volume.[9,25,26] Notably, no relation was found between age and cognitive functioning after ECT.[8,27] In addition, several factors related to ECT administration were negatively associated with cognitive functioning during ECT, that is, bilateral electrode placement, brief pulse width and higher stimulus dose of ECT.[10,28–30]

The mechanisms by which change in cognitive functioning during and after a course of ECT may occur are largely unknown.[31] One hypothesis is that cognitive functioning after ECT is impacted by larger temporary ECT-induced changes in hippocampus volume.[32] Another hypothesis is that there is an analogue with the pathogenesis of delirium: evidence from delirium research suggests that clinical factors such as inflammation, endocrine abnormalities, and oxidative stress can lead to transient disturbances in

cognitive functioning by interacting with pre-existent degenerative changes of the brain.[33,34] Studies have found a relationship between increased levels of peripheral inflammatory markers, postoperative delirium and postoperative cognitive dysfunction.[35] We hypothesize that comparable mechanisms as in delirium influence cognitive functioning in depressed patients treated with ECT, and that the extent of the pre-existent inflammatory state of the depressed brain may further explain the variability in observed cognitive functioning prior to, during and after ECT.

Aims of the study

This study aims to investigate whether an inflammatory profile relates to cognitive functioning prior to, during and directly after a course of ECT. We hypothesize that higher levels of inflammatory markers are associated with lower cognitive functioning during and after ECT. The Mood Disorders in Elderly treated with Electroconvulsive Therapy (MODECT) multicentre study provides an excellent opportunity to study the interplay between inflammatory markers and cognitive functioning in depressed persons. Previously it was shown that low-grade inflammation has a favourable effect on treatment response, e.g. moderately elevated CRP levels were associated with increased remission rates in depressed patients treated with ECT.[36,37] Serum levels of C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-10 (IL-10) and tumour necrosis factor-alpha (TNF-α) - biomarkers that to our knowledge have not been studied yet in relation to cognitive functioning during and after a course of ECT in a larger sample of older depressed patients - were chosen for further exploration.

METHODS

Study sample

110 older (>55 years) patients were included in this naturalistic prospective cohort study. Patients were selected between January 2011 and December 2013 from an inpatient population, referred for ECT, from the Department of Old Age Psychiatry of GGZ inGeest, Amsterdam, the Netherlands, and University Psychiatric Center KU Leuven, Belgium.[38] Informed consent was obtained from all patients. The study protocol was approved by the ethical review board of the Amsterdam UMC and UPC Leuven and adhered the declaration of Helsinki. The clinical trial was registered at www.ClinicalTrials.gov with identifier: NCT02667353. Diagnosis of severe unipolar depression according to the DSM-IV was made by a psychiatrist and confirmed with the Mini International Neuropsychiatric Interview (MINI).[39,40] Exclusion criteria were a major neurological illness including prior diagnosis of dementia. Patients with missing

Table 1. Baseline characteristics of older depressed patients treated with ECT

	Total n = 97
Sociodemographics	
Age, years, mean (SD)	73.1 (8.1)
Women, No. (%)	65 (67.0)
Level of education, years, median (IQR)	9.0 (3.0)
Inclusion site, Amsterdam/Leuven, No. (%Amsterdam)	54/43 (55.7)
Baseline MMSE, mean (SD), n = 82	24.1 (5.1)
MMSE after ECT, mean (SD)	26.2 (3.8)
Baseline MADRS, mean (SD)	33.8 (9.0)
Somatic morbidity	
Cardiovascular diseases, No (%)	22 (23.4)
No. of chronic diseases, median (IQR)	1.0 (2.0)
Current smoking, No. (%), n = 82	21 (26.3)
Current alcohol use, No. (%), n = 91	24 (26.7)
ECT characteristics	
ECT sessions, median (IQR)	11.0 (6.0)
Switch to bilateral ECT, No. (%)	29 (30.2)
Remission, No. (%)	64 (67.4)
Use of antidepressants, No. (%), n = 82	15 (18.5)
Use of antipsychotics, No. (%), n = 82	7 (8.6)
Biomarkers, median (IQR)	
CRP, n = 90	1.7 (3.9)
IL-6, n = 91	2.7 (3.6)
IL-10, n = 93	0.9 (0.6)
TNF-_, n = 96	4.5 (1.7)

SD = standard deviation, IQR = inter quartile range, No. = number, MADRS = Montgomery Åsberg depression rating scale, CRP=C-reactive protein, IL-6 = interleukin-6, IL-10 = interleukin-10, TNF-α = tumour necrosis factor- α

serum cytokine or CRP values were excluded from analysis (n=13). Attrition was not differential for age, sex, baseline depression severity, baseline cognitive functioning and level of education.

Assessments

Global cognitive functioning was screened with the MMSE[41], and was assessed prior to ECT, weekly during ECT and one-week after ECT (range 0-30). The outcome was defined as 1) the mean MMSE score one-week prior to the course of ECT, 2) the course of weekly MMSE scores during treatment, and 3) the mean MMSE score one-week after the course of ECT.

Biomarkers

Marker selection was based on their relevance in previous studies on inflammation and depression. CRP is most widely used as a clinical marker for inflammation.[42] Both IL-6 and TNF-α are widely used in psychiatric research as potential biomarkers involved in depression.[43–45] IL-10 is an anti-inflammatory cytokine[46] with strong deactivating properties of the inflammatory host response in case of excessive inflammation.[47] IL-10 is able to inhibit the production of proinflammatory cytokines such as IL-6 and TNF-α.[46] Serum samples were collected prior to ECT between 07h30 and 09h30 and were stored at -85°C until assayed. Analyses of inflammatory markers were performed as described before.[36] In short, serum levels of CRP were determined with the High Sensitive (CRPhs) kit (Cobas CRPHA; Cat. No. 04628918 190). Serum levels of IL-6, IL-10 and TNF-α, were simultaneously determined using a 3-step multiplex digital immunoassay, the Simoa Human Cytokine 3-Plex A assay kit (Quanterix; cat.# 101160). Intra-assay and inter-assay reproducibility were 4.3% and 5.9% for IL-6, 3.9% and 5.3% for IL-10 and 4.2% and 5.3% for TNF-α, respectively. All determinations were performed at the Clinical Chemistry department of Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands.

Characteristics

Depressive symptoms were evaluated using the Montgomery Åsberg rating scale (MADRS, range 0-60).[48] Remission was defined as a score < 10. Information on age, sex, inclusion site, the level of education in years, current smoking (yes/no), current alcohol use (yes/no) and somatic history including presence of cardiovascular diseases and the number of chronic diseases (cardiovascular disease, hypertension, chronic respiratory disease, diabetes mellitus, and arthrosis) were collected in a semi-structured interview. Antidepressant and antipsychotic medication use during ECT and

ECT characteristics including electrode placement and the total number of treatment sessions were collected during treatment.

ECT procedure

Brief pulse ECT was administered twice weekly using the Thymatron System IV (maximum energy 200%, 1008 mCoulombs) according to Dutch guidelines.[49] A titration protocol was used to determine the seizure threshold. Higher stimulus dose relative to seizure threshold is a risk factor for cognitive impairment[28], therefore all patients received a stimulus dose six times the seizure threshold for unilateral stimulation and 2.5 times the seizure threshold for bilateral stimulation. Seizure duration shorter than 20 seconds (motor activity) or 25 seconds (EEG activity) was considered inadequate after which the dose was raised. Treatment was continued until remission was achieved or until there was no further improvement. Switch to bilateral stimulation (n=31) was made when no clinical improvement occurred after six right unilateral treatments or when clinical condition worsened, i.e. increased suicidality, dehydration or an increased MADRS score. Psychotropic medications were tapered off within two weeks prior to ECT or were kept stable during the ECT course if necessary.

Statistical analyses

Baseline characteristics are reported as means with standard deviation (SD), median with interquartile range (IQR) and as percentages. In post hoc analysis, differences between patients with low and high levels of TNF-α were tested using independent samples t-tests, Mann-whitney U tests and $\chi 2$ tests. Statistical significance was set at $p < 0.05$. Normality (of the residuals) was assessed by the visual exploration of the data. Outliers were excluded according to Q1 – 3*IQR and Q3 + 3*IQR to avoid bias as a result of acute infection (CRP: n=7, IL-6: n=6, IL-10: n=4, TNF-α: n=1). Dichotomized values of the biomarkers - using the median value as the cut-off – were used to draw figures and to compare MMSE values within low and high inflammation groups. The mean MMSE values prior to and directly after a course of ECT were analysed using independent samples t-tests. We used a linear mixed model analysis to explore the association between biomarkers and longitudinal MMSE data (weekly scores) during treatment. The advantages of using a longitudinal mixed model instead of a linear regression analysis is that it allows for correlation between repeated measures, that is, inclusion of weekly MMSE scores rather than a change score, and it allows for multivariate analyses. After week seven most patients had finished ECT (84/97, 86.6%) and although mixed models are capable of processing missing values, the estimated models for week 8 and further are based on merely 13.3% of actual measures, therefore we used solely the first seven

weeks of MMSE measures. Subsequently, linear regression analysis was used to estimate the association between CRP, IL-6, IL-10 and TNF-α with cognitive functioning prior to and directly after a course ECT. All analyses were adjusted for age, sex, baseline MADRS score, and baseline cognitive functioning. All analyses were adjusted for cardiovascular diseases, smoking and alcohol use as lifestyle factors can be associated with inflammation and/or cognition.[50–56] In the linear regression models, effect size (Cohen's f^2) was calculated from delta R2 and was interpreted as a small: $f^2 = 0.02$, medium $f^2 = 0.15$ or large $f^2 = 0.30$ effect.[57] No correction for multiple testing was applied as a clear a priori hypothesis was assessed.[58] The explained variance was estimated in multivariate analyses. Sensitivity and specificity were calculated. Switching to bilateral electrode placement can result in decreased cognitive functioning during and after ECT[10], therefore post hoc analysis was performed excluding all patients that switched to bilateral ECT during treatment. To rule out an influence of improvement of depressive symptoms on the association between inflammatory markers and cognitive functioning the interaction terms between inflammatory markers, remission, and change in MADRS were examined post hoc. If interaction terms were significant ($p<0.1$), analyses were repeated stratified. Multicollinearity was evaluated using Variance Inflation Factors (VIF) where a VIF > 2 indicates multicollinearity between covariates. Statistical analyses were performed using SPSS version 23 and STATA version 15.

RESULTS

In total, 97 patients were included in the analysis. The mean age was 73.1 years (SD ± 8.1), Table 1. In total, 35.1% of patients (34/97) received bilateral ECT of which 88.6% of patients (30/34) after six unilateral sessions. Overall, 22 patients used either antipsychotic or antidepressant medication.

Cognitive functioning prior to a course of ECT

The mean MMSE score at baseline was 24.1 (SD ± 5.1) and was significantly lower in patients with higher levels of IL-6 ($t=2.5$, df 59.5, $p = 0.02$) and TNF-α ($t=3.2$, df 46.2, $p=<0.01$; Figure 1). In adjusted linear regression analysis, an association with a small to medium effect was found between higher levels of TNF-α at baseline and lower cognitive functioning prior to start of ECT: $f^2 = 0.06$, see Table 2. No significant association was found with CRP, IL-6, and IL-10, and effect sizes were small: $f^2 = 0.05$, 0.03 and 0.02 respectively. The fully adjusted model including TNF-α explained 14.8% of the variance of cognitive functioning prior to a course of ECT (adjusted R2 = 0.148).

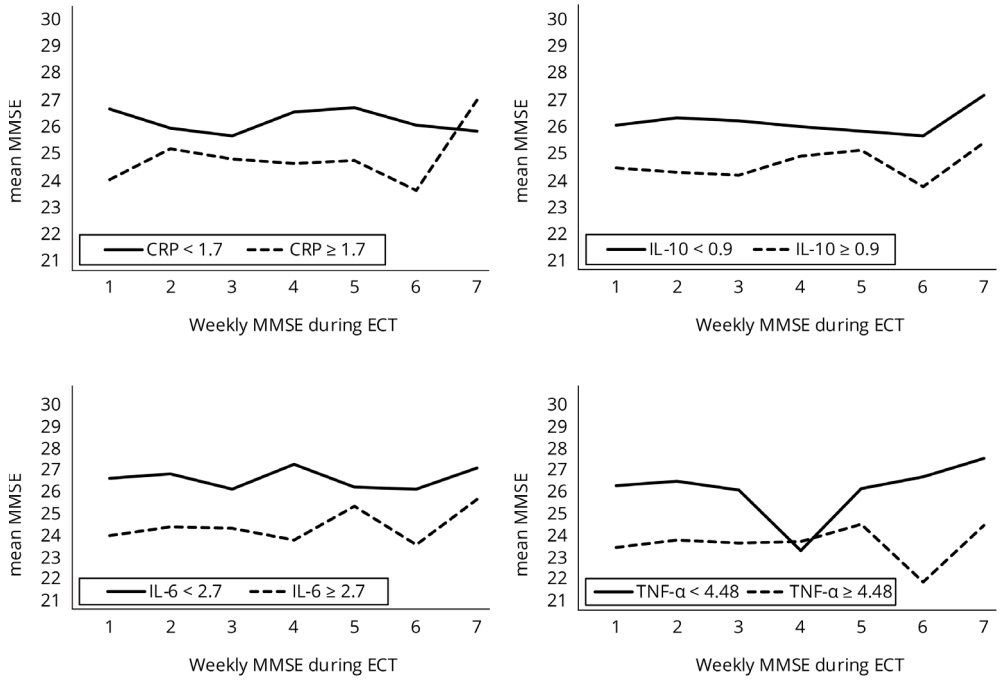

Figure 1. Mean weekly MMSE scores during the first seven weeks of ECT in depressed, older patients, stratified for low and high levels of CRP, IL-6, IL-10 and TNF-α.

Cognitive functioning during ECT

Notably, a drop in MMSE is seen in Figure 1 at week 4 of treatment in patients with lower levels of TNF-α only. In linear mixed model analysis including the first seven weeks of ECT, adjusted for age, sex, depression severity, baseline MMSE scores, cardiovascular diseases, smoking and alcohol use, higher levels of IL-10 and TNF-α were associated with lower MMSE scores, see Table 2.

Cognitive functioning directly after a course of ECT

The mean MMSE score directly after ECT was 26.2 (SD ± 3.8) and was significantly lower in patients with higher levels of IL-6 ($t = 2.3$, $df\ 86$, $p = 0.03$). We found a significant association between higher levels of CRP at baseline and cognitive functioning directly after a course of ECT in adjusted linear regression analysis: $f^2 = 0.10$, see Table 2. The associations

between the baseline cytokine levels and cognitive functioning after ECT were nonsignificant and the sizes of the effect were small: IL-6: f^2 = <0.01, IL-10: f^2 = 0.04, TNF-α: f^2 = 0.003. The fully adjusted model including CRP explained 24.9% of the variance of cognitive functioning directly after a course of ECT (adjusted R2 = 0.249).

In post hoc analysis, patients that switched to bilateral ECT during treatment were excluded. The results remained similar for findings during ECT. The results after ECT altered slightly, that is, in the multivariate models, the association between IL-10, TNF-α and cognitive functioning altered to a significant association

Table 2. Association between baseline biological markers and cognitive functioning in linear regression and mixed model analyses in older depressed patients receiving ECT

	Univariate		**Multivariate**	
	β (95% CI)	*p*	β (95% CI) [1]	*p*
Prior to start of ECT				
CRP	-0.41 (-0.79 to -0.02)	0.04	-0.30 (-0.77 to 0.16)	0.2
IL-6	-0.29 (-0.59 to 0.01)	0.1	-0.18 (-0.62 to 0.26)	0.4
IL-10	-1.29 (-3.51 to 0.94)	0.3	0.08 (-2.48 to 2.62)	0.9
TNF-α	-1.02 (-1.78 to -0.26)	<0.01	-1.05 (-2.04 to -0.06)	0.04
During ECT				
CRP	-0.33 (-0.60 to -0.06)	0.02	-0.18 (-0.42 to 0.06)	0.1
IL-6	-0.22 (-0.43 to -0.00)	0.05	0.10 (-0.06 to 0.26)	0.2
IL-10	-2.85 (-4.44 to -1.26)	<0.01	-2.08 (-3.22 to -0.95)	<0.01
TNF-α	-0.69 (-1.13 to -0.24)	<0.01	-0.65 (-1.07 to -0.22)	<0.01
Directly after a course of ECT				
CRP	-0.30 (-0.58 to -0.02)	0.04	-0.51 (-0.93 to -0.09)	0.02
IL-6	-0.15 (-0.39 to 0.08)	0.2	0.06 (-0.30 to 0.43)	0.7
IL-10	-1.98 (-3.64 to -0.33)	0.02	-1.84 (-3.82 to 0.14)	0.1
TNF-α	-0.44 (-0.91 to 0.04)	0.1	-0.57 (-1.40 to 0.25)	0.2

[1] adjusted for age, gender, depression severity at baseline, presence of cardiovascular disease, smoking, alcohol use and MMSE at baseline. Number of patients range from 58 to 94 because of missing data for some covariates.
Abbreviations. CI = confidence interval, CRP=C-reactive protein, IL-6 = interleukin-6, IL-10 = interleukin-10, TNF-α = tumour necrosis factor- α

(TNF-α: β = -1.18; 95%CI = (-1.48 to -0.88), f^2 = 0.83, IL-10: β = -3.86; 95%CI = (-4.77 to -2.95), f^2 = 0.87). Values for sensitivity and specificity did not exceed 80% for any of the inflammatory markers. No multicollinearity was found between covariates (VIF <2). No interaction effects were found between inflammatory markers and remission of depression, nor between CRP, IL-6, TNF-α and change in MADRS score both during and after a course of ECT. The interaction effect between IL-10 and change in MADRS score was significant. However, in stratified analysis, similar results were found, that is, no significant association was found between baseline IL-10 and cognitive functioning after a course of ECT. In post hoc analysis, similar remission rates were found between patients with low or high levels of TNF-α. Patients with higher levels of TNF-α were older and had more chronic diseases, see supplemental content.

DISCUSSION

In this naturalistic cohort, we investigated whether higher levels of inflammatory markers are related to cognitive functioning. We hypothesized that inflammatory markers such as CRP, IL-6, IL-10 and TNF-α are associated with lower cognitive functioning in depressed patients treated with ECT. Previously, in this cohort it was shown that moderately elevated levels of CRP are associated with higher remission rates whereas IL-6, IL-10 and TNF-α are not.[36] Here, we find that 1) higher levels of TNF-α are associated with lower cognitive functioning prior to the start of ECT, 2) higher baseline levels of IL-10 and TNF-α are significantly associated with lower cognitive functioning during the first seven weeks of ECT, even when controlling for baseline MMSE and 3) higher baseline levels of CRP are associated with cognitive functioning directly after a course of ECT. Patients with higher levels of CRP, IL-6, IL-10 and TNF-α only partially overlap. Our findings suggest that especially patients with higher levels of TNF-α not only experience a decreased cognitive functioning prior to the start of ECT but also are more vulnerable to lower cognitive functioning during a course of ECT.

Cognitive symptoms in older depressed patients and inflammation

This is the first study to examine inflammatory markers and cognition in patients treated with ECT. Our finding that patients with higher levels of TNF-α are more likely to experience lower cognitive functioning prior to ECT suggests that severe depression with inflammation is associated with cognitive symptoms. Why do inflammatory depressed patients experience lower cognitive functioning? An analogy with the pathophysiological mechanism of delirium is proposed. Evidence from delirium research suggests that the

presence of inflammation can lead to disturbances in cognitive functioning by interacting with pre-existent degenerative changes of the brain and that peripheral inflammation can induce the release of inflammatory markers in the central nervous system.[33,35] In depression, the presence of low-grade peripheral inflammation in combination with degenerative changes (in older patients) or a pre-existent inflammatory state of the brain may explain the variability in observed cognitive symptoms in depressed patients. Our findings are in line with other studies in which an association between higher levels of inflammatory markers and cognitive impairment in older, healthy or depressed subjects was found.[59–66] However, there are many conflicting reports showing a lack of association between inflammatory markers and cognitive impairment in older, healthy or depressed subjects.[67–69] An explanation for the inconsistency in these findings could be the different composition of participants under study - for example, participants with less severe depressive symptoms - and different use of cognitive measures (global cognitive functioning scale versus specific cognitive domains). There are no comparable studies in older depressed patients treated with ECT. Our findings further strengthen the idea that cognitive functioning in older persons is influenced by an inflammatory process.

Cognitive side effects of ECT and inflammation

The mechanism by which cognitive side effects during and directly after a course of ECT occur is largely unknown. In contrast to our expectations, there was no decline in MMSE at group level during ECT. Our findings may suggest that depressed patients with higher levels of inflammatory markers are more vulnerable to lower cognitive functioning – although only small changes occurred - during and after a course of ECT. However, as this association was also found prior to ECT, it is difficult to arrive at any conclusions with regard to the effect of ECT on this association.

Future implications

Monitoring inflammatory processes to predict cognitive functioning in depressed patients prior to and after a course of ECT seems possible based on the current data. Although the sensitivity and specificity when using inflammatory markers to predict cognitive functioning were low, the percentage of variance explained by the multivariate model was 25%. Administration of anti-inflammatory medication during ECT can significantly reduce levels of TNF-α as is shown in patients with bipolar depression.[70] If our findings are confirmed, such treatment strategies could be of additional value for improvement of cognitive functioning prior to, during and after a course of ECT. Future investigations of the effect of anti-inflammatory treatment on cognitive functioning in depression are

merited. Moreover, to further explore whether changes in inflammatory markers during ECT affect cognitive functioning during and after ECT, future studies should include longitudinal measurements of inflammatory markers. Just like in delirium research[34] multiple pathways may be complementary in cognitive functioning in depressed patients. Therefore, a suggestion for future studies may be to combine inflammatory markers with other (imaging) biomarkers in developing a combined risk score for lower cognitive functioning during and after a course of ECT. In addition, to further explore whether changes in cognitive functioning are driven by specific cognitive domains, future studies should include more specific and sensitive neuropsychological instruments rather than solely the MMSE.

Limitations

Notably, the following strengths and limitations should be considered. The prospective study design allowed us to collect a substantial set of clinical data from which putative confounders were selected. We used the MMSE – widely used to measure global cognitive functioning - as a scale to measure cognitive functioning. It has shortcomings such as test-retest effects, a ceiling effect, the lack of ability to assess specific cognitive domains, and it may lack sensitivity to detect small changes, especially in patients with vascular brain changes.[71–75] Despite the ceiling effect, we found a significant association between inflammatory markers and cognitive functioning suggesting the effect may be larger if we had used a more sensitive test. Moreover, one of the difficulties in investigating cognitive functioning during ECT is the influence of depression itself on cognitive performance. In this study, the influence of ECT on cognitive functioning may be underreported because of the synchronous improvement of depressive symptoms and cognition.[76] This study used pre-ECT inflammatory markers to investigate the association with cognitive functioning pre-, during and after ECT. Including longitudinal inflammatory biomarkers would have allowed us to control for depression-related changes in inflammation. Also, it is to be determined whether the differences in weekly MMSE scores between patients with lower and higher inflammatory markers (ranging from 0.5 to 2.5 points) is of clinical relevance to patients. No corrections for multiple testing were performed and, although the analysis were all hypothesis driven, this still may have affected the type I error of this study. Finally, other factors may impact on cognition such as anaesthesia itself[9], pulse width[77], and stimulus dose of ECT.[28] To minimize the influence of these factors on our findings, all patients received equal ratios of stimulus dose relative to seizure threshold and all received brief pulse ECT.

Conclusion

Previously low-grade inflammation was found to be associated with increased remission rates in our sample of 97 depressed older patients treated with ECT. This current study suggests that baseline inflammatory processes are associated with lower cognitive functioning prior to ECT (TNF-α), and predispose for (further) cognitive dysfunction during (TNF-α and IL-10) and after (CRP) a course of ECT. Future studies could provide more in-depth on the role of inflammation on the cognitive symptoms of depression, and the effectivity of (add-on) anti-inflammatory treatment to improve these symptoms during an ECT course.

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SUPPLEMENTAL MATERIAL

Supplemental Table. Group characteristics of older depressed patients with low (< 4.48 pg/ml) or high levels of TNF-α treated with ECT (n = 96).

	Low TNF-α n = 56	**High TNF-α** n = 40	*p*
Socio-demographics			
Age, years, mean (SD)	70.8 (7.7)	76.4 (7.7)	<0.01
Women, No. (%)	36 (64.3)	29 (72.5)	0.4
Baseline MMSE, mean (SD), n = 81	25.5 (3.9)	21.7 (5.9)	<0.01
MMSE after ECT, mean (SD)	26.8 (3.6)	25.4 (4.0)	0.1
Baseline MADRS, mean (SD)	33.9 (8.1)	33.7 (10.3)	0.9
Remission, No. (%)	39 (69.6)	25 (64.1)	0.6
Somatic morbidity			
Cardiovascular diseases, No (%)	9 (16.4)	13 (33.3)	0.1
No. of chronic diseases, median (IQR)	1.0 (1.0)	1.0 (1.0)	0.02
Current smoking, No. (%), n = 82	13 (30.2)	8 (21.6)	0.4
Current alcohol use, No. (%), n = 91	15 (27.3)	9 (25.7)	0.9
ECT characteristics			
ECT sessions, median (IQR)	10.5 (6.0)	11.5 (7.0)	0.8
Switch to bilateral ECT, No. (%)	15 (26.8)	14 (35.0)	0.6
Use of antidepressants, No. (%), n = 82	7 (16.3)	8 (21.1)	0.6
Use of antipsychotics, No. (%), n = 82	3 (7.0)	4 (10.5)	0.6

SD = standard deviation, IQR = inter quartile range, No. = number, MADRS = Montgomery Åsberg depression rating scale, TNF-α = tumour necrosis factor- alpha

CHAPTER 7

IMPACT OF INFLAMMATION ON COGNITIVE FUNCTIONING AFTER ELECTROCONVULSIVE THERAPY IN OLDER DEPRESSED PATIENTS WITH AND WITHOUT WHITE MATTER HYPERINTENSITIES

Brief report

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ABSTRACT

Objectives

Should we treat older, depressed patients with white matter hyperintensities (WMH) with electroconvulsive therapy (ECT)? WMH, inflammation, depression and cognitive functioning are suggested to be intertwined. Hence, this study investigates whether the presence of WMH alters the association between inflammatory markers and cognitive functioning in depressed patients treated with ECT.

Methods

Cognitive functioning was screened using the Mini-Mental State Examination after a course of ECT in 79 older depressed patients. Serum samples (C-reactive protein [CRP], interleukin-6 [IL-6], interleukin-10 [IL-10] and tumour necrosis factor-alpha [TNF-α]) and 3T magnetic resonance imaging were obtained in the week before the start of ECT.

Results

In linear regression analyses, stratified for presence of moderate to severe WMH, both IL-10 and TNF- α were significantly associated with lower cognitive functioning in patients with WMH.

Conclusions

These findings suggest that patients with WMH are more vulnerable to lower cognitive functioning after ECT when inflammation is present.

INTRODUCTION

Should we treat older, depressed patients with white matter hyperintensities (WMH) with electroconvulsive therapy (ECT)? ECT is the most effective treatment for depression[1], however, practitioners are often reluctant to start ECT because of the risk of transient[2] cognitive effects after a course of ECT. Previously, in this cohort[3], a relationship was found between higher baseline levels of inflammatory markers and lower cognitive functioning in older depressed patients before, during and after electroconvulsive therapy (ECT). In line with these findings, although still inconclusive, studies suggest an association between cognitive functioning and inflammation in both depressed and healthy persons.[4] A potential underlying factor linking inflammation with cognition might be white matter pathology as studies have found associations between WMH, cognitive functioning and depression[5,6], as well as between WMH and inflammation. For example, in post-operative delirium research, it was found that patients with pre-operative WMH had an increased risk of developing delirium[7], which is a disorder characterized by temporary profound changes in cognitive functioning, suggesting that a brain with WMH is more vulnerable to inflammation.

Here, we expand on our earlier findings and investigate whether, in older depressed patients, the association between inflammatory markers and cognitive functioning is different for patients with moderate to severe WMH. For many practitioners, the cognitive side effects of ECT remain a concern. Hence, it is particularly interesting to explore the association between inflammatory markers and cognitive functioning directly after a course of ECT in an ECT cohort with older depressed patients. A better understanding of the underlying factors contributing to lower cognitive functioning may lead to potential targets for prevention.

METHODS

Study overview

Data were collected from two psychiatric hospitals, GGZ inGeest in the Netherlands, and the University Psychiatric Center KU Leuven in Belgium. All included patients were diagnosed with unipolar major depression, aged 55 years and older and referred for ECT. Excluded were patients with a history of major neurological illness including stroke and dementia. All procedures involving patients were approved centrally by the Ethical Review Board of the Amsterdam University Medical Centre and subsequently by the ethical review board of the Leuven University Hospitals. Written consent was obtained

from all participants. Here we present data from a subgroup (n=79) from a previously described cohort study.[7] The median number of ECT administrations was 11.0 (interquartile range: 6.0). ECT was continued until a Montgomery Åsberg Depression Rating Scale score of less than 10 was reached at two consecutive ratings or until no further improvement in clinical condition was seen after at least six unilateral and six bilateral ECT sessions.

Inflammatory markers

The selection of potential relevant inflammatory markers is based on availability and findings on the relevance of these markers in studies to date. Serum cytokine and C-reactive protein (CRP) levels were measured in the week before the start of ECT. Interleukin-6 (IL-6), interleukin-10 (IL-10) and tumour necrosis factor-alpha (TNF-α) were determined using the Simoa Human Cytokine 3-Plex immunoassay. CRP was determined using the Cobas CRPHA kit. All determinations were performed at the Clinical Chemistry department of Amsterdam UMC, Vrije Universiteit, Amsterdam.

Cognitive functioning

Cognitive functioning was screened using the Mini-mental State Examination (MMSE, score range 0-30) directly after a course of ECT, e.g. one week after the last ECT session.

White matter hyperintensities

MRI was performed prior to ECT. Structural WMH were rated using the Age-Related White Matter Changes (ARWMC) scale as the sum score of ten brain regions, subsequently ranked in two groups: 1) no or few structural white matter hyperintensities (WMH; score 0-9) and 2) moderate to severe WMH (score 10-30). All MRI images were rated by an independent neuroradiologist.

Statistical analyses

The association between inflammatory markers and MMSE score was investigated using linear regression analyses and was stratified for the presence of WMH. All analyses were adjusted for age, gender, baseline depression severity, baseline cognitive functioning, years of education, smoking, alcohol use and presence of cardiovascular diseases. Results are reported as β-coefficient with a 95% confidence interval (CI). A p-value <0.05 was considered significant.

RESULTS

The mean age of the sample was 72.9 years (SD±8.4). Patients without structural WMH (n=52) had a mean MMSE score of 26.8 (SD±3.5) directly after a course of ECT compared to a mean score of 25.0 (SD±4.6) in patients with structural WMH (n=27). In fully adjusted linear regression analyses, stratified for presence of structural WMH, both IL-10 and TNF- α were significantly associated with lower cognitive functioning directly after a course of ECT in patients with WMH (IL-10: β = -4.11 [CI: -6.43; -1.79], TNF-α: β = -2.57 [CI: -4.05; -1.08]). This association was not found for any of the inflammatory markers and cognitive functioning in patients without WMH, see Table 1. The association between CRP prior to ECT and cognitive functioning after ECT in patients with WMH lost its significance after adjustment for possible confounders including the presence of cardiovascular diseases.

Table 1. Linear regression analyses. Association between inflammatory markers and cognitive functioning directly after a course of ECT divided in patients with no or few structural white matter hyperintensities (WMH) (n=52) and patients with moderate to severe WMH (n=27), in older depressed patients.

Predictor variable	**Univariate**		**Multivariable**	
	β (95% CI)	*p*	β (95% CI)	*p*
No structural WMH				
CRP	-0.04 (-0.41 to 0.33)	0.8	-0.18 (-0.75 to 0.39)	0.5
IL-6	-0.05 (-0.36 to 0.26)	0.7	-0.05 (-0.46 to 0.56)	0.8
IL-10	-0.81 (-2.94 to 1.31)	0.5	-1.17 (-3.37 to 1.02)	0.3
TNF-α	-0.07 (-0.55 to 0.69)	0.8	0.36 (-0.73 to 1.46)	0.5
Moderate to severe WMH				
CRP	-0.75 (-1.38 to -0.11)	0.02	-0.60 (-1.34 to 0.15)	0.1
IL-6	-0.62 (-1.27 to 0.04)	0.1	-0.61 (-1.35 to 0.14)	0.1
IL-10	-4.26 (-7.46 to -1.06)	0.01	-4.11 (-6.43 to -1.79)	<0.01
TNF-α	-2.02 (-3.19 to -0.85)	<0.01	-2.57 (-4.05 to -1.08)	<0.01

Multivariable model: adjusted for age, gender, years of education, MMSE at baseline, depression severity at baseline, presence of cardiovascular disease, smoking and alcohol use.

CI = confidence interval, CRP = C-reactive protein, IL-6 = interleukin-6, IL-10 = interleukin-10, TNF-α = tumour necrosis factor-α

CONCLUSIONS

Previously, we suggested that ECT is more effective in patients with signs of inflammation (CRP levels 3 to 10 mg/L).[9] In addition, in the same cohort, we found that patients with higher levels of several inflammatory markers prior to ECT showed lower cognitive functioning both before, during and after a course of ECT in depressed older patients (Carlier et al - submitted). With the present study, we wanted to investigate whether the association between cognitive functioning and inflammation is different for patients with or without WMH.

Our findings suggest that WMH form an underlying factor in the relationship between inflammation prior to ECT and cognition after a course of ECT. No association was found between inflammatory markers prior to ECT and cognitive functioning after a course of ECT in depressed patients without white matter hyperintensities further strengthening this hypothesis. In line with our findings, two previous studies have described a lower cognitive function in depressed patients with WMH, although cognitive functioning was measured during ECT.[10,11] These findings suggest that patients with white matter hyperintensities are more vulnerable to lower cognitive functioning after ECT when inflammation is present, whereas older depressed patients with inflammation tend to have higher remission rates, as mentioned above.[9] In addition, patients with WMH have similar response and remission rates as patients without WMH[12], therefore the presence of WMH does not oppose ECT. Further research is needed to determine whether these findings can be utilized in the prevention of cognitive symptoms in depression and/or cognitive effects in ECT. Limitations of this study are the use of the MMSE to measure cognitive functioning as it has a known ceiling effect and test-retest effects. In addition, adjustment for cardiovascular diseases and smoking may have caused an underestimation of the association between inflammation and cognitive functioning.

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CHAPTER 8

SUMMARY AND GENERAL DISCUSSION

SUMMARY

Background

This thesis's main objective was to expand current knowledge on biomarkers in ECT-treatment to contribute to future personalized treatment of late-life depression. The first part of this work examined the pattern of biomarkers during a course of ECT and the association between biomarkers and treatment outcome. The second part explored the association between inflammatory markers, cognitive functioning, and white matter hyperintensities. In the past 30 years, over 8000 studies concerning ECT have been conducted. Still, at present, we cannot distinguish which persons will respond to antidepressant medication or ECT, resulting in a stepwise treatment protocol similar for all depressed patients. ECT is recommended in depressed persons only after two trials of antidepressants have failed [1]. In this thesis, we explored whether biomarkers can assist in identifying patients that are more likely to respond to ECT and are more likely to experience cognitive side effects. The main results are summarized and discussed below. Finally, methodological considerations, implications for clinical practice, and recommendations for future research are addressed.

PART I:
Biomarkers and depression

S100 calcium-binding protein

One biomarker of interest included in this work was S100 calcium-binding protein (S100B). S100B is a protein that is expressed by microglial cells (astrocytes and oligodendrocytes) and has various functions in neuronal plasticity and apoptosis. It can be used as a marker of neuroplasticity.[2] Increasingly, it is thought that neuroplasticity is disrupted in depression.[3–5] S100B is suggested as a biomarker indicative of depression (a disease state marker), as it is found elevated in episodes of major depression.[6,7] Neuroplasticity, on the other hand, is also considered a potential working mechanism of ECT. Volume increases in the hippocampus, amygdala and cingulate cortex have been observed after ECT.[8–10] In **Chapter 2** we investigated whether S100B was a state marker of depression and whether it was associated with favourable ECT outcome within the MODECT cohort of 110 older depressed patients receiving ECT. Changes in pre- and post-ECT levels of S100B were compared between remitters and

nonremitters. Logistic and Cox regression analyses were used to determine whether S100B was associated with remission of depression. There was no significant decrease in levels of S100B after ECT in both remitters and nonremitters, which made it less likely that S100B was a state marker of depression. Patients with intermediate levels of S100B (between 33 ng/L and 53 ng/L) before ECT had favourable treatment outcome compared to patients with lower or higher levels of S100B. They were also more likely to remit from depression over time. Despite the association between S100B and remission, sensitivity and specificity were low, therefore, S100B is not considered an eligible biomarker of ECT outcome.

Inflammation

Other biomarkers of interest included in this work were inflammatory markers. When peripheral inflammatory markers cross the blood-brain barrier, they can activate microglia, and, therefore, may impact both neuroinflammation and neuroplasticity.[11,12] Over the past years, compelling evidence has associated depression with inflammation. First, higher levels of inflammatory markers are found in patients with depression.[13–21] In late-life depression in specific, inflammatory markers are found in nearly half of the patients.[22] Second, it is suggested that markers of inflammation play a role in the pathophysiology of depression as they activate microglia who in their turn promote neuroinflammation, oxidative stress and activate the kynurenine pathway.[11,12,23,24] The kynurenine pathway can cause neurotoxicity and is often found activated in depressed patients.[11] Third, findings suggest an association between peripheral inflammatory markers and treatment response[25–27] or treatment non-response.[28,29] In **Chapter 3**, we investigated whether there was an association between pre-treatment levels of inflammatory markers and ECT outcome. We found that moderately elevated levels (3 to 10 mg/L) of CRP were associated with higher remission rates of depression and an increased speed of symptom decline after ECT. A remission rate of 83.9% in patients with a CRP of 3 to 10 mg/L was found comparedwith a remission rate of 61.1% in those with CRP levels lower than 3 mg/L. Per ECT session we estimated a decline of 3.2 MADRS points (Montgomery Åsberg Depression Rating Scale) in the moderately elevated CRP group compared to 2.3 MADRS points in the low CRP group. No consistent associations were found between IL-6, IL-10, TNF-α and ECT outcome. We concluded that older depressed patients with low-grade inflammation benefit more from ECT than patients without low-grade inflammation.

Subsequently, we were interested in whether ECT has an anti-inflammatory effect. Previous studies found an increase in leucocytes, interleukin-1 and IL-6 after a single ECT administration suggesting an acute immune response.[30–32] After repeated ECT administrations, although the number of studies was limited, levels of interleukin-5, IL-6, and TNF-α tended to fall.[30,32] To investigate whether ECT has an anti-inflammatory effect, we examined changes in inflammatory markers during and after ECT. In **Chapter 4**, the pattern of CRP, IL-6, IL-10, and TNF-α was examined among depressed older patients in the MODECT study. Small to medium effect sizes were found for a decrease in CRP and IL-6 after ECT. No differences were found in the pattern of inflammatory markers between responders and non-responders, and between remitters and non-remitters of depression. We concluded that a possible decrease in inflammatory markers after ECT is not associated with ECT outcome and that the anti-inflammatory effect of ECT could not be confirmed.

Apathy

Late-life depression has been associated with white matter changes[33] and white matter changes in turn have been associated with apathy.[34–36] Despite the overlap between motivational symptoms of depression and apathetic symptoms, apathy is considered an independent behavioural syndrome.[37] Apathy is a known contributing factor to a decreased quality of life.[38] In **Chapter 5** we investigated whether there was an association between vascular burden and the course of apathy in 73 apathetic patients treated with ECT within the MODECT study. Vascular burden included the presence of vascular disease, diabetes mellitus, smoking, and white matter hyperintensities. MRI data on white matter hyperintensities were available in 52 patients only. After ECT, 50 patients (68.5%) remitted from depression. Of these 50 patients, 52.0% still suffered from clinically evident apathy. Of the patients that did not remit from depression (n=23), 78.3% experienced apathy. No association was found between persistent apathy and vascular burden. First, we concluded that apathy may not be relieved by successful treatment with ECT and needs a distinctive approach. Second, the persistent apathy symptoms measured in our cohort might have been, in some patients, residual symptoms of depression. Finally, we concluded that apathy in depressed patients may be different from apathy in non-depressed patients as, in contrast to other studies, we found no association between vascular burden and apathy. This idea is strengthened by studies suggesting a strong link between higher levels of CRP and apathy in non-depressed patients[39] but not in depressed patients.[40]

PART II:
Biomarkers and cognition

Apart from examining ECT outcome such as remission, getting closer to personalized depression treatment also involves investigating the side effects of ECT. For many ECT practitioners, cognitive side effects after ECT remain a concern. In **Chapter 6**, we examinedwhether inflammatory markers could help us to identify which patients are more prone to developing cognitive side effects during and after ECT. Cognitive functioning was assessed with the Mini-Mental State Examination (MMSE). Pre-treatment inflammatory processes were associated with lower cognitive functioning prior to ECT (TNF-α). As this association was present before start of ECT, we were unable to disentangle the explicit influence of inflammatory markers on cognitive functioning during and after ECT. In line with our findings, a known risk factor for lower cognitive functioning during and after ECT is poor baseline cognitive functioning.[41,42] Previous studies suggested an association between cognitive impairment and higher levels of inflammation in older, healthy or depressed subjects.[43–47] We suggested that similar processes are involved in cognitive functioning during ECT, that is, that lower cognitive functioning pre-ECT is associated with higher levels of inflammation. These patients are subsequently predisposed for cognitive dysfunction during and after a course of ECT, although the attributable effect of ECT remains uncertain.

Apart from the link between inflammation and cognition, studies have suggested a link between lower cognitive functioning, depression and white matter hyperintensities.[48] Therefore, to expand the findings of **Chapter 6**, we investigated whether the presence of white matter hyperintensities altered the association between inflammatory markers and cognitive functioning in older depressed patients treated with ECT (**Chapter 7**). To specifically examine ECT influences, we looked at cognitive functioning after ECT for this analysis. In stratified linear regression analyses, both higher levels of IL-10 and TNF-α pre-ECT were associated with lower cognitive functioning after a course of ECT in patients with white matter hyperintensities, compared with no association in patients without white matter hyperintensities. We concluded that patients with white matter hyperintensities are more vulnerable to lower cognitive functioning after ECT only when inflammation is present.

Overall conclusions

The main objective of this thesis was to expand current knowledge on biomarkers in ECT-treatment to contribute to future personalized treatment of late-life depression. The first part aimed to explore biomarkers and treatment outcome. The second part aimed to explore biomarkers and cognitive functioning. We can conclude that older depressed patients with a profile of low-grade inflammation or intermediate levels of S100B who receive ECT have higher chances of remission of depression. However, we also conclude that both CRP and S100B are not eligible biomarkers for ECT outcome as their sensitivity and specificity were low. In general, a useful biomarker should have a sensitivity (for detecting therapy outcome) and a specificity (for discriminating between outcomes) of at least 80%.[49] Vascular brain changes, that is, white matter hyperintensities, are not associated with persistent apathy after ECT. Higher levels of inflammation before start of ECT are associated with lower cognitive functioning. This association remains during and after ECT, however, it seems that patients with inflammation and white matter hyperintensities are in particular vulnerable to developing lower cognitive functioning after ECT.

METHODOLOGICAL CONSIDERATIONS

This thesis is based on the Mood Disorders in Elderly treated with ECT study (MODECT), a multi-site, naturalistic, prospective cohort study on older (>55 years) patients treated with ECT. Strengths of the MODECT are its relatively large sample of clinical patients with a major depressive disorder (n=110) and its comprehensive set of data including brain imaging and blood samples. A few considerations have to be kept in mind when interpreting the findings of this thesis. Generalization of these results towards younger patients, outpatients or patients with mild or moderate depression is not indisputable. Moreover, the study may lack power when comparing subgroups of patients.

Next, within MODECT, the collection of a substantial set of clinical data allowed us to adjust for putative confounders, nonetheless, the risk of residual confounding has to be considered in observational cohort studies. Moreover, psychotropic medication could not be tapered off in all patients causing a possible confounding effect albeit inconsistent findings exist on whether psychotropic medication influences inflammation[50] and levels of S100B.[51] Likewise, MODECT was not primarily set-up for inflammatory research, therefore, data on the concurrent use of anti-inflammatory medication is missing. In addition, body mass index-data was absent in nearly half of the patients and comprehending that adipose tissue is highly correlated with levels of S100B[52] and circulating levels of inflammatory cytokines[53] this limits our findings. Moreover, acute infections in patients were not reported. To exclude these patients, we have excluded timepoint samples with CRP levels that were three standard deviations above and below interquartile range or CRP levels above 10 mg/L, as is best practice in scientific literature.[54] In the concerning studies (**Chapters 3,4, and 6**), analyses are reported both with and without extreme values to give a complete image of the data.

Some of the measures used in MODECT should be reconsidered for future research. For example, the Apathy Scale by Starkstein et al.[55] is validated in older patients with dementia and Parkinson's disease, but not in patients with depression. An alternative could be the Apathy Evaluation Scale by Marin et al.[56] In addition, the Mini-Mental State Examination[57] measures global cognitive functioning but has shortcomings such as not being able to distinguish between different cognitive domains and it may lack sensitivity to detect small changes.[58,59]

We should note that the biomarkers described in this thesis indicate peripheral inflammation and not central inflammation. Studies measuring levels of inflammation

in cerebrospinal fluid (csf) are scarce, however, studies have found increased levels of inflammation in csf[60] and a high correlation between levels of peripheral CRP and csf CRP in depressed patients[61] suggesting that peripheral markers can indicate central inflammation. In this study, circulating inflammatory markers were measured which indicate the presence of inflammation over a prolonged period.[62] Levels of circulating inflammatory markers are thought to be less affected by genetic factors than stimulated inflammatory markers.[63,64] The latter provides information on a patient's cytokine production capacity. It is important to keep in mind that cytokine levels show a high degree of heterogeneity across studies[28,29] because they are sensitive to multiple outside signals such as disease, infection, and smoking behaviour. A recent study has meta-analyzed this variability in patients with depression; IL-6 and TNF-α variability was similar for controls and depressed patients.[21] Variability of CRP in depressed patients, however, was significantly reduced compared to controls suggesting CRP to be a rather homogenous inflammatory marker in depression.

Regarding longitudinal follow-up, it should be considered that in the apathy study (**Chapter 5**), we were unable to include 4-week follow up measurements because of high numbers of loss to follow up (62%). Future research should examine longer periods after ECT to examine whether apathy is a residual symptom of depression.

Finally, for every study, a consideration was made whether to correct for multiple testing. In **Chapters 3, 6, and 7**, no correction for multiple testing was made, even though the analyses included four biomarkers (CRP, IL-6, IL-10, TNF-α). By making this decision, the risk of a type-I error (rejecting a true null-hypothesis) increased.[66] To support our findings, effect sizes were calculated in Chapters 3 to 6 using Cohen's f^2 or Cohen's d.[67]

IMPLICATIONS FOR CLINICAL PRACTICE AND THEORY

This thesis aimed to explore the association between biomarkers and ECT outcome, and biomarkers and cognitive functioning, and to expand knowledge for future personalized treatment of late-life depression.

Theory on antidepressants versus ECT

Studies involving untreated patients or patients receiving antidepressant medication found associations between levels of inflammation, persistence of symptoms, and treatment resistance.[28,68,69] A recent meta-analysis regarding 15 inflammatory markers found no, except one, associations between inflammatory markers and response to antidepressants.[29] Our study found no association with treatment resistance. In contrast, we found an association between inflammation and favourable ECT outcome. Other studies found a better ECT outcome in patients with higher levels of IL-6[70] or TNF-α.[71] These findings may suggest that patients with higher levels of inflammation are more likely to respond to ECT than to antidepressant medication. Currently, treatment of depression follows a stepped-care model. A more personalized approach would be to use a stratified care plan in which treatment modalities are chosen based on biomarker profile. An example of a stratified care plan is given in Figure 1. However, it should be kept in mind that the inconsistencies between findings from antidepressant medication trials and ECT trials may also be explained by the different patients under study. Patients receiving ECT are frequently patients with treatment-resistant and severe depression which can influence levels of inflammation, and therefore may confound the findings from antidepressant- and ECT trials. Consequently, our findings only apply to depressed patients from a population comparable to the one in this thesis. Randomized studies including depressed patients with and without inflammation receiving different treatment modalities are necessary before a stratified care model can be realized.

We demonstrated that remitters of depression had higher levels of CRP before start of ECT. It has long been thought that depression is a heterogeneous disorder and that different subtypes require different treatment approaches. Our findings may suggest that inflammatory subtypes of depression respond well to ECT. One previously proposed subtype in depressed adults is the immune-metabolic subtype; a subtype related to inflammatory markers, female gender, higher BMI, metabolic syndrome , and atypical symptoms of depression (weight gain and increased appetite).[68,72–78] These 'atypical' symptoms of depression are less prevalent in older persons than in adults.[74,79,80] In addition,as predictors of ECT response include 'typical' (melancholic) symptoms of

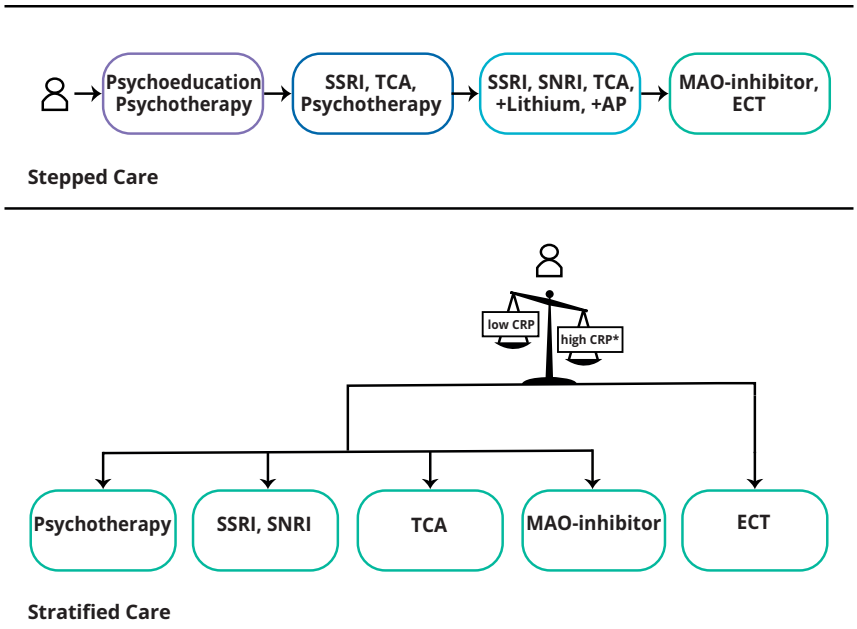

Figure 1. An example of an older patient following a stepped care or a (hypothetical) stratified care plan in which treatment modalities are chosen stepwise or based on biomarker profile.
* These findings apply only to older patients with severe depression comparable with the population in this thesis, findings need replication

depression such as decreased appetite, hyposomnia and psychomotor retardation, patients referred for ECT can be expected to have more melancholic symptoms than patients in studies involving other treatment modalities. Therefore, the patients under study in this thesis may differ from the patients in the above mentioned studies and may share another immunological subtype of depression than the immune-metabolic subtype. To find out if the patients receiving ECT have the same depression subtype as the immune-metabolic patients, further research is needed. A recent study by Lynall et al.[81] suggests that separate subgroups exist within the inflammatory subtype. They found two subgroups, both with higher levels of CRP and IL-6, however, with different immune cell profiles. Group 1 showed higher numbers of adaptive immune cells (T cells and B cells), for example, memory cells reacting to previously experienced stress or infection. Group 2 showed higher numbers of innate immune cells (monocytes and neutrophils), that is, an

acute reaction to stress or infection. These findings suggest that different aetiologies may account for different immunological subtypes of depression.

Although our findings suggest that patients with higher levels of inflammation tend to respond well to ECT, we could not confirm an anti-inflammatory effect of ECT. Newer antidepressant treatments such as add-on infliximab, minocycline[25,82], and ketamine appear to have more anti-inflammatory properties and should therefore be included in further research regarding immunological subtypes of depression. As an example, a trial will start soon at the Amsterdam University Medical Center, where patients with the immune-metabolic subtype of depression will be treated with the anti-inflammatory medicine Celecoxib. So, why do we think that patients with higher inflammatory markers respond well to ECT? Maybe increased inflammation in depressed patients merely reflects older age[83], more severe depression[84] or psychomotor retardation[85], all factors associated with better ECT outcome. Another possibility is that ECT does have a central anti-inflammatory effect that is not observed in our peripheral measurements. Kranaster et al.[86] found a decrease of an innate immunity regulator protein (MIF) in the csf of patients that remitted from ECT suggesting a reduction in central cytokine production after a course of ECT. Furthermore, they found that patients with increased levels of baseline sCD14 - a marker of glial activation - had higher chances of responding to ECT similar to our finding of S100B. This may suggest that glial activity and immune cell activity pre-ECT is beneficial in further treatment, though the mechanism behind this benefit remains unknown.

Subsequently, our study demonstrated a link between cognition and inflammation in depressed patients with or without treatment of ECT. Previous research has found that patients with white matter hyperintensities have similar remission rates as patients without white matter hyperintensities[87] and patients with higher inflammation have even higher remission rates after ECT[70,71] despite the increased risk of lower cognitive functioning. The mechanism behind inflammation, cognition and white matter hyperintensities is unknown. We propose a possible analogy with delirium, a disorder where disturbances in cognitive functioning are caused by inflammation interacting with degenerative changes in the brain (for example, an ageing brain).[88,89] Assumed that this hypothesis is correct, it is possible that in older depressed patients, lower cognitive functioning is caused by a pre-existent (possibly caused by depression) inflammatory state of the brain. As described earlier, peripheral inflammatory factors can induce microglial cytokine production causing neuroinflammation.[11] Inflammatory markers on the brain side of the blood-brain barrier (BBB) can weaken BBB integrity[65,90], therefore, patients with

pre-existent inflammation may have a different crossover of immune cells during ECT compared with patients with an intact BBB possibly causing more cognitive symptoms. As for clinical implications, monitoring inflammatory processes to predict cognitive functioning in depressed patients prior to and after a course of ECT seems possible based on the current data. In addition, monitoring inflammatory processes during depression can assist in understanding, and possibly treating, observed cognitive symptoms.

FUTURE RESEARCH

Our study demonstrated higher remission rates in patients with moderately elevated levels of CRP and intermediate levels of S100B. Previous research in turn suggested older age, psychomotor symptoms and psychotic symptoms as features associated with remission.[71,91,92] Therefore, a future step could be to see whether these features combined reach a reasonable test sensitivity and specificity to be able to predict ECT outcome.

Also, a large number of patients does not respond to the current existing treatments for depression. Several studies have identified differential symptom clusters of depression[74,80,93,94], nevertheless, studies still tend to include heterogeneous samples of depressed patients also because inconsistent symptom clusters are found across studies.[95,96] The previously mentioned subtypes were all identified using latent class analysis. Other techniques have been used such as machine learning allowing for large data samples and low costs.[93] For example, national electronic health records could be used in the future to identify symptom clusters in depressed patients receiving ECT and their outcomes.

Next, it would be of interest to investigate the prevalence of different symptom clusters across different age groups. For example, as low-grade inflammation has been associated with older age[63], inflammatory symptom clusters may be more common in late-onset depression. Moreover, studies should investigate the effectiveness of medication and ECT in several subtypes of depression, for instance, by clustering depressive symptoms and randomly assigning patients to treatment modalities including placebo, an SSRI and ECT. An example of a similar type of study is that of Bondar et al.[97] who identified two symptom clusters in depressed adolescents, of which one symptom cluster responded to psychotherapy and fluoxetine and the other symptom cluster did not, both in comparison to placebo.

Another step would be to perform clinical trials and cohort studies within different symptom clusters of depression. For example, low-grade inflammation (CRP > 3mg/L) occurs in 27% of all depressed patients.[13] Future studies could use a match-mismatch design in which patients with and without low-grade inflammation are allocated to 'matched' and 'mismatched' treatment modalities. We would expect patients with higher levels of inflammation to respond better to ECT and patients with lower inflammation to respond better to antidepressants.

Moreover, a meta-analysis of Kohler et al.[98] showed that both add-on therapy and monotherapy with anti-inflammatory medication can reduce depressive symptoms. Most effective were add-on NSAIDs, monotherapy cytokine inhibitors, add-on glucocorticoids, and add-on or monotherapy minocycline, although studies are heterogeneous and small. Almost all studies up to date have included a heterogeneous group of depressed patients. As approximately one-third of patients have increased inflammation[13], studies should target those patients specifically. Further research could be in the form of large randomized controlled trials in which depressed patients with increased inflammation are allocated to several anti-inflammatory medications and placebo. Cytokine-inhibitors such as Tocilizumab (anti-IL-6), Siltuximab (anti-IL-6), and Adalimumab (anti-TNF-α) could be useful as they specifically target measurable peripheral markers. Outcome measures should not include general depression severity only, but also include cytokine associated behavioural symptoms such as symptoms of anhedonia and anxiety.[99–101] It is also important to monitor adverse events of anti-inflammatory medication, especially in older persons.

Furthermore, our results suggest that patients with depression with higher levels of inflammatory markers experience lower cognitive functioning. Further research is needed to explore whether reducing inflammation can increase cognitive functioning in depression and ECT. Future studies should focus on the effect of anti-inflammatory treatment on cognitive functioning in depression.

In Chapter 2, we found that patients with low levels of S100B had less favourable responses to ECT. S100B is used as a marker of neuroplasticity and has various functions in neuroplasticity itself.[2] If our findings are confirmed, the next step would be to explore treatment strategies that may increase the level of S100B and whether this contributes to responsiveness to depression treatment. From a biological perspective, there is a link between inflammation and neuroplasticity. For example, peripheral inflammation can activate microglia who in their turn promote the release of cytokines.[12] How both these processes are involved in depression needs further investigation.

Finally, the working mechanism of ECT remains unclear. In Chapter 3 we were unable to confirm an anti-inflammatory effect of ECT. So why do patients with higher levels of inflammation and S100B respond better to ECT in particular? The hypothesis that ECT activates microglia cells by inducing an acute immune response should be tested in clinical samples of depressed patients with the use of PET scans that can measure microglia activation and blood samples measuring immune activation.

Concluding remarks

The main message that can be drawn from this thesis is that inflammatory processes seem to be involved in both cognitive functioning and response to treatment and that ECT is effective in treating patients with increased levels of inflammatory markers. However, as anti-inflammatory properties of ECT could not be confirmed, other antidepressant treatment modalities that fall outside the scope of this thesis may be even more effective. Inflammatory biomarkers can aid in future personalized depression treatment perhaps by implementing stratified care instead of stepped care. For example, if findings are confirmed, ECT could be started in patients with higher levels of inflammation before starting second or third trials with antidepressant medication. Inflammatory biomarkers may also be useful in developing new antidepressant treatment strategies such as (add-on) anti-inflammatory medication to reduce depressive symptoms[98] and improve cognitive functioning.

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CHAPTER 9

NEDERLANDSE SAMENVATTING

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Achtergrond

Dit proefschrift had als doel de huidige kennis over biomarkers en elektroconvulsie therapie (ECT) te vergroten en zo bij te dragen aan toekomstige gepersonaliseerde behandeling van depressie op oudere leeftijd, met name bij patiënten die met ECT worden behandeld. Het eerste deel van dit werk onderzocht het patroon van biologische markers tijdens ECT en de associatie tussen biologische markers en uitkomst van behandeling. Het tweede deel onderzocht de associatie tussen biomarkers, cognitief functioneren en witte stof hyperintensiteiten. In de afgelopen 30 jaar zijn er meer dan 8000 onderzoeken naar ECT uitgevoerd en ondanks al die studies kunnen we op dit moment niet onderscheiden welke patiënten het beste zullen reageren op antidepressiva en welke op ECT. Er wordt gebruik gemaakt van een stapsgewijs behandelprotocol dat voor alle depressieve patiënten gelijk is. ECT wordt pas aanbevolen bij patiënten die onvoldoende opgeknapt zijn op ten minste twee antidepressieve medicamenten. In dit proefschrift onderzochten we of biologische markers kunnen helpen in het onderscheid welke patiënten zullen verbeteren op ECT (Deel I) en wie er meer kans hebben op cognitieve bijwerkingen (Deel II). De belangrijkste resultaten worden hieronder samengevat en besproken.

DEEL 1:
Biomarkers en depressie

S100 calciumbindend eiwit

Een van de biomarkers die we onderzocht hebben is het calciumbindende eiwit S100 (S100B). S100B is een eiwit dat tot expressie wordt gebracht door microgliacellen (astrocyten en oligodendrocyten) en dat verschillende functies heeft bij neuronale plasticiteit en apoptose. Het kan onder andere worden gebruikt als een marker van neuroplasticiteit. In toenemende mate wordt gedacht dat neuroplasticiteit verstoord is bij depressie en uit meerdere studies blijkt dat depressieve patiënten hogere S100B-waarden hebben dan gezonde controles. Ook wordt neuroplasticiteit beschouwd als een mogelijk onderdeel van het werkingsmechanisme van ECT doordat is aangetoond dat het volume van de hippocampus, amygdala en cingulaire cortex toenemen na ECT. In Hoofdstuk 2 onderzochten we of S100B een marker was voor de aanwezigheid van depressie en of S100B geassocieerd was met een gunstige ECT-uitkomst binnen het MODECT-cohort van 110 oudere depressieve patiënten die allemaal met ECT behandeld

werden. Veranderingen in S100B-waarden voor- en na ECT werden vergeleken tussen patiënten die van hun depressie herstelden (remitters) en patiënten die niet herstelden (niet-remitters). Er was geen significante afname in S100B-waarden na ECT bij zowel remitters als niet-remitters, waardoor het minder waarschijnlijk is dat S100B een marker is die depressie aantoont. Patiënten met S100B waarden tussen 33 ng/L en 53 ng/L vóór ECT hadden een gunstiger behandelresultaat vergeleken met patiënten met lagere of hogere waarden van S100B. Ze hadden ook meer kans om na verloop van tijd van hun depressie te herstellen. Ondanks de associatie tussen S100B en remissie, waren de sensitiviteit en specificiteit laag, daarom wordt S100B niet beschouwd als een geschikte biomarker voor ECT-uitkomst.

Inflammatie

Andere biomarkers die centraal stonden in dit proefschrift waren de inflammatoire markers; C-reactief proteïne (CRP), interleukine-6 (IL-6), interleukine-10 (IL-10) en tumornecrosefactor-alfa (TNF-α). Deze markers kunnen de bloed-hersenbarrière passeren en daar vervolgens (door activatie van microglia) zowel neuro-inflammatie als neuroplasticiteit beïnvloeden. Depressie en ontsteking worden de laatste jaren veelvuldig met elkaar in verband gebracht. Ten eerste worden er bij patiënten met depressie hogere inflammatoire markers gevonden dan in gezonde controlepersonen. In de groep patiënten met een depressie op latere leeftijd blijkt dit bij bijna de helft van de patiënten het geval. Ten tweede wordt gesuggereerd dat inflammatoire markers een rol spelen in de pathofysiologie van depressie. Ten derde lijkt er een verband te zijn tussen perifeer aanwezige inflammatoire markers en behandelrespons of non-respons.

In Hoofdstuk 3 hebben we onderzocht of er een verband bestond tussen de hoogte van inflammatoire markers vooraf aan de behandeling met ECT en de behandelrespons. We zagen dat matig verhoogde waarden (3 tot 10 mg/L; laaggradige inflammatie) van CRP geassocieerd waren met hogere remissiecijfers van depressie en een snellere symptoomafname tijdens ECT. Er werd een remissiepercentage van 83,9% gevonden bij patiënten met een CRP van 3 tot 10 mg/L, vergeleken met een remissiepercentage van 61,1% bij patiënten met een CRP-spiegel lager dan 3 mg/L. Per ECT-toediening schatten we een afname van 3,2 MADRS-punten (Montgomery Åsberg Depression Rating Scale) in de matig verhoogde CRP-groep vergeleken met 2,3 MADRS-punten in de lage CRP-groep. Er werden geen consistente associaties gevonden tussen IL-6, IL-10, TNF-α en behandelrespons. We concludeerden dat oudere depressieve patiënten met laaggradige inflammatie meer baat hebben bij ECT dan patiënten zonder laaggradige inflammatie.

Vervolgens wilden we onderzoeken of ECT een ontstekingsremmend effect heeft. Eerdere studies vonden een toename van leukocyten, interleukine-1 en IL-6 na één enkele ECT-toediening passend bij een acute immuunreactie. Na herhaalde ECT-toedieningen, hoewel het aantal onderzoeken beperkt was, leken interleukine-5, IL-6 en TNF-α juist te dalen. Om te onderzoeken of ECT een ontstekingsremmende werking heeft, onderzochten we het patroon van CRP, IL-6, IL-10 en TNF-α tijdens en na ECT (Hoofdstuk 4). We vonden kleine tot middelgrote effectgroottes voor een afname van CRP en IL-6 na ECT. Er werden geen verschillen gevonden in het patroon van inflammatoire markers tussen responders en non-responders, en tussen remitters en non-remitters van depressie. We concludeerden dat een mogelijke afname van inflammatoire markers na ECT niet geassocieerd is met behandelrespons en dat het ontstekingsremmende effect van ECT niet kon worden aangetoond in deze studie.

Apathie

Depressie op latere leeftijd is in verband gebracht met veranderingen in witte hersenstof en veranderingen in witte hersenstof zijn op hun beurt in verband gebracht met apathie. Ondanks dat er een overlap bestaat tussen motivationele symptomen van depressie en apathische symptomen, wordt apathie beschouwd als een onafhankelijk syndroom. Van apathie is bekend dat het de kwaliteit van leven verlaagd. In Hoofdstuk 5 hebben we onderzocht of er een verband was tussen vasculaire belasting en het beloop van apathie bij 73 apathische patiënten die met ECT werden behandeld binnen het MODECT-cohort. Vasculaire belasting omvatte de aanwezigheid van vaatziekte, diabetes mellitus, roken en hyperintensiteit van witte stof. MRI-gegevens over witte stof hyperintensiteiten waren beschikbaar bij 52/73 patiënten. Na ECT waren 50 patiënten (68,5%) hersteld van hun depressie. Van deze 50 patiënten leed 52,0% nog aan apathie. Van de patiënten die niet herstelden van hun depressie (n = 23) ervoer 78,3% apathie. Er werd geen verband gevonden tussen aanhoudende apathie en vasculaire belasting. Ten eerste concludeerden we dat een succesvolle ECT behandeling niet altijd gepaard gaat met een afname van apathie en dat de behandeling van apathie mogelijk een andere aanpak vereist. Ten tweede was het mogelijk dat de aanhoudende apathiesymptomen in ons cohort restsymptomen waren van depressie. Tot slot leek het erop dat apathie bij depressieve patiënten verschilt van apathie bij niet-depressieve patiënten omdat wij in tegenstelling tot vele andere studies geen associatie vonden tussen apathie en vasculaire belasting. Dit idee wordt versterkt door studies waarbij een sterk verband wordt gevonden tussen hoge CRP-waarden en apathie bij niet-depressieve patiënten, maar geen verband bij depressieve patiënten.

DEEL II:
Biomarkers en cognitie

Om dichter bij een gepersonaliseerde depressie behandeling te komen is het, naast het onderzoeken van de behandelrespons, ook belangrijk om onderzoek te doen naar de bijwerkingen van ECT. Voor veel betrokkenen, zowel patiënten, hun naasten en behandelaars blijven cognitieve bijwerkingen na ECT een punt van zorg. In Hoofdstuk 6 onderzochten we of inflammatoire markers ons konden helpen identificeren welke patiënten meer vatbaar zijn voor het ontwikkelen van cognitieve bijwerkingen tijdens en na ECT. Het cognitief functioneren werd beoordeeld met de Mini-Mental State Examination (MMSE). Ontstekingswaarden vooraf aan de behandeling bleken geassocieerd met een verminderd cognitief functioneren voorafgaand aan ECT (TNF-α). Omdat deze associatie aanwezig was vóór de start van ECT, konden we de additionele invloed van ECT op deze associatie niet goed ontwarren. Een bekende risicofactor voor een lager cognitief functioneren tijdens en na ECT is een slecht cognitief functioneren op baseline. Dit is in lijn met onze bevindingen. Ook vonden eerdere studies een verband tussen cognitieve stoornissen en hogere ontstekingswaarden bij oudere, gezonde of depressieve proefpersonen. We denken dat vergelijkbare processen betrokken zijn bij cognitief functioneren tijdens ECT, dat wil zeggen, dat een lager cognitief functioneren vooraf aan ECT geassocieerd is met hogere ontstekingswaarden. Deze patiënten zijn vervolgens vatbaar voor cognitieve disfunctie tijdens en na ECT, hoewel het toe te schrijven effect van ECT onzeker blijft.

Naast het verband tussen inflammatie en cognitie, komt in meerdere studies naar voren dat er ook een verband bestaat tussen lager cognitief functioneren, depressie en witte stof hyperintensiteiten. Daarom hebben we in Hoofdstuk 7 onderzocht of de aanwezigheid van hyperintensiteiten in witte stof de gevonden associatie in Hoofdstuk 6 (tussen inflammatoire markers en cognitief functioneren) versterkt. Om de invloed van ECT te onderzoeken hebben we voor deze analyse gekeken naar het cognitief functioneren na ECT. Het verband tussen hogere waarden van IL-10 en TNF-α vooraf aan ECT en een lager cognitief functioneren na ECT werd alleen gevonden bij patiënten mét witte stof hyperintensiteiten. We concludeerden dat patiënten met witte stof hyperintensiteiten alleen kwetsbaarder zijn voor een lager cognitief functioneren na ECT als er inflammatie aanwezig is.

Algemene conclusies

Het doel van dit proefschrift was het vergroten van de kennis over biomarkers en elektroconvulsie therapie (ECT) en zo bij te dragen aan toekomstige gepersonaliseerde behandeling van depressie op oudere leeftijd. In dit proefschrift onderzochten we onder andere C-reactief proteïne (CRP), als inflammatie-marker, en calciumbindend eiwit S100 (S100B), als neurotrofine. De belangrijkste boodschap die uit dit proefschrift getrokken kan worden, is dat ontstekingsprocessen betrokken lijken te zijn bij zowel het cognitief functioneren tijdens een depressie als de uitkomst van ECT. Oudere depressieve patiënten met laaggradige inflammatie of intermediaire S100B-waarden die behandeld worden met ECT, hebben een grotere kans op herstel van depressie. We concluderen echter ook dat zowel CRP als S100B op zichzelf onvoldoende sensitiviteit en specificiteit hebben om ECT-uitkomst te kunnen voorspellen. Van bruikbare biomarkers wordt verwacht dat ze een sensitiviteit (voor het detecteren van ECT-uitkomst) en een specificiteit (voor het discrimineren tussen uitkomsten) hebben van ten minste 80%. De eventuele ontstekingsremmende werking van ECT kon in dit proefschrift niet worden bevestigd. Het kan dus zijn dat andere depressiebehandelingen - die buiten het bestek van dit proefschrift vallen - nog effectiever zijn bij patiënten met laaggradige inflammatie dan ECT.

Concluderend kan gesteld worden dat biomarkers kunnen bijdragen aan toekomstige gepersonaliseerde behandeling voor depressie. In de huidige richtlijn wordt een ‘stepped-care’ benadering gevolgd waarbij patiënten eerst lichte interventies krijgen en bij onvoldoende herstel zwaardere interventies. Een alternatief zou kunnen zijn om bij depressie voor ‘stratified-care’ te kiezen waarbij de behandeling wordt afgestemd op de kenmerken van de patiënt. Als onze bevindingen worden bevestigd zou bijvoorbeeld een patiënt met laaggradige inflammatie eerder in aanmerking komen voor ECT dan in het huidige model. Ook zou toekomstig onderzoek zich kunnen richten op strategieën om depressie te behandelen en het cognitief functioneren te verbeteren door bijvoorbeeld additioneel te behandelen met ontstekingsremmende medicatie.

LIST OF PUBLICATIONS

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Carlier, A., Rhebergen, D., Veerhuis, R., Schouws, S., Oudega, M., Eikelenboom, P., Bouckaert, F., Sienaert, P., Obbels, J., Stek, M.L., Exel, E. van*, Dols, A.* Inflammation and cognitive functioning in depressed older adults treated with electroconvulsive therapy; a prospective cohort study. J Clin Psych., 2021, 82:0-0.

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ABOUT THE AUTHOR

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Angela Carlier was born on the 5th of April 1989 in Amsterdam, the Netherlands. After graduating from her bilingual secondary education at the Vechtstede College in Weesp in 2007, she started studying biomedical sciences at the Vrije Universiteit in Amsterdam. This is where her interest in scientific research began. As part of her internship, she examined whether shared aetiology could explain the comorbidity between borderline personality disorder and attention deficit hyperactivity disorder. After receiving her bachelor's degree in 2010 she moved to Maastricht to start her double master program (Physician – Clinical Investigator) in which research and medicine are combined. In her research internship, she set up a pilot study examining repeated carbon dioxide inhalations as a treatment for patients with panic disorder.

After receiving her medical degree in 2014 she started working as a medical doctor at the Department of Old Age Psychiatry at De Nieuwe Valerius, GGZ inGeest in Amsterdam. After one year she started her residency in psychiatry at the University Medical Centre, location AMC, in Amsterdam under the supervision of dr. Jitschak Storosum and dr. Pelle de Koning. During her residency, she started her PhD research under the supervision of Prof. dr. Max Stek, dr. Eric van Exel, and dr. Didi Rhebergen. In July 2020, Angela completed her residency and started working as a psychiatrist at Pro Persona in Nijmegen. She is also a member of the editorial board at De Jonge Psychiater.

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DANKWOORD

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